

60 REC'D PCT/PTO 05 JUL 2001

FORM PTO-1390 (Modified)
(REV 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

210100USPCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/868894

INTERNATIONAL APPLICATION NO.
PCT/JP00/00018

INTERNATIONAL FILING DATE
06 January 2000

PRIORITY DATE CLAIMED
07 January 1999(earliest)

TITLE OF INVENTION
CYCLIC COMPOUND

APPLICANT(S) FOR DO/EO/US
TANIGUCHI Kiyoshi et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Notice for Consideration of Documents Cited in International Search Report/Notice of Priority/PCT/IB/304
PCT/IB/308

U.S. APPLIC

09/868894

INTERNATIONAL APPLICATION NO.

PCT/JP00/00018

ATTORNEY'S DOCKET NUMBER

210100US0PCT

24. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000.00
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00
- ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =**CALCULATIONS PTO USE ONLY**

\$860.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).

\$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	17 - 20 =	0	x \$18.00
Independent claims	1 - 3 =	0	x \$80.00
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>

\$0.00

TOTAL OF ABOVE CALCULATIONS =

\$860.00

☐ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.

\$0.00

SUBTOTAL =

\$860.00

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

\$0.00

TOTAL NATIONAL FEE =

\$860.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

\$0.00

TOTAL FEES ENCLOSED =

\$860.00

Amount to be:
refunded \$
charged \$

- a. ☒ A check in the amount of \$860.00 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 15-0030 A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

**22850**

Surinder Sachar
Registration No. 34,423

SIGNATURE

Norman F. Oblon

NAME

24,618

REGISTRATION NUMBER

DATE

July 5 2001

DESCRIPTION

CYCLIC COMPOUND

5 Field of the Invention

The present invention relates to new compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new compounds and pharmaceutically acceptable salts thereof which are useful
10 as inhibitors of matrix metalloproteinases (hereinafter to be referred to as MMP) or the production of tumor necrosis factor α (hereinafter to be referred to as TNF α), to pharmaceutical compositions comprising the same, to use of the same as medicaments, and to methods for using the same
15 therapeutically in the treatment and/or the prevention of MMP- or TNF α -mediated diseases.

Background Art

Some compounds to be useful as metalloproteinase inhibitors, or the like are known (WO 97/20824, etc.).

20 Disclosure of the Invention

One object of the present invention is to provide new and useful cyclic compounds and pharmaceutically acceptable salts thereof, and to provide a process for preparing said new cyclic compound and salts thereof, which have
25 pharmacological activities such as MMP- or TNF α - inhibitory activity and the like.

Another object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said cyclic compound or a pharmaceutically
30 acceptable salt thereof.

A further object of the present invention is to provide use of said cyclic compounds and pharmaceutically acceptable salts thereof as medicaments for prophylactic and therapeutic treatment of MMP- or TNF α -mediated diseases.

35 A still further object of the present invention is to

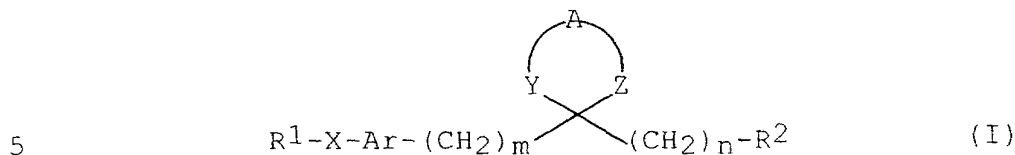
provide a method for using the same for the treatment and/or the prevention of MMP- or TNF α -mediated diseases in mammals, especially humans.

The compounds of the present invention have inhibitory activity on MMP or the production of TNF α , and are useful for the treatment and/or prevention of diseases such as stroke, arthritis, cancer, tissue ulceration, decubitus ulcer, restenosis, periodontal disease, epidermolysis bullosa, scleritis, psoriasis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases caused by the production of TNF α .

There are a number of structurally related metalloproteases which effect the breakdown of structural proteins. Matrix-degrading metalloproteases, such as gelatinase (MMP-2, MMP-9), stromelysin (MMP-3) and collagenase (MMP-1, MMP-8, MMP-13), are involved in tissue matrix degradation and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g., osteoarthritis and rheumatoid arthritis, etc.), cerebral disease (e.g., stroke, etc.), tissue ulceration (e.g., corneal, epidermal and gastric ulcerations, etc.), abnormal wound healing, periodontal disease, bone disease (e.g., Paget's disease and osteoporosis, etc.), tumor metastasis or invasion and HIV-infection.

A tumor necrosis factor is recognized to be involved in many infections and autoimmune diseases. Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock.

The object compounds of the present invention are novel and can be represented by the following formula (I):



in which R^1 is lower alkyl, halogen, optionally substituted heterocyclic group or optionally substituted aryl,

10 R^2 is carboxy, protected carboxy or amidated carboxy,

Ar is optionally substituted aryl or optionally substituted heterocyclic group,

A is lower alkylene,

15 X is oxa or a single bond,

Y is thia, sulfinyl or sulfonyl,

Z is methylene, thia, sulfinyl or sulfonyl,

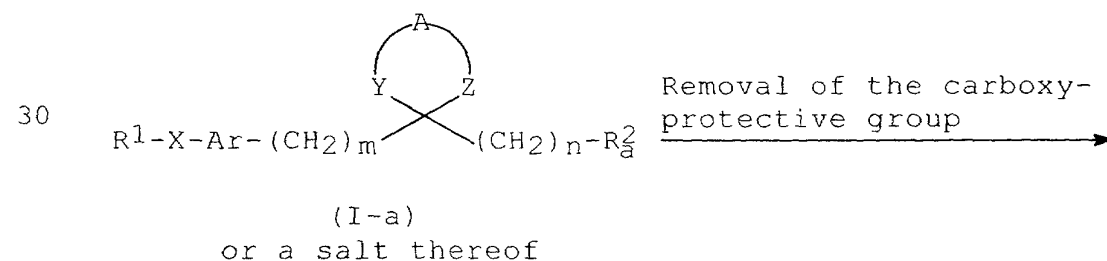
m and n are each an integer of 0 to 6, and

$1 \leq m+n \leq 6$,

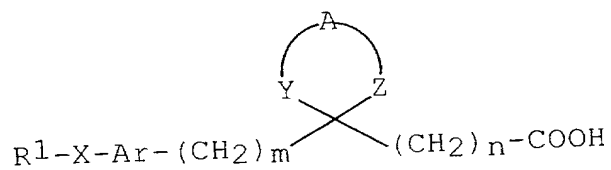
20 and its salt.

The object compounds of the present invention can be prepared by the following processes.

25 Process 1

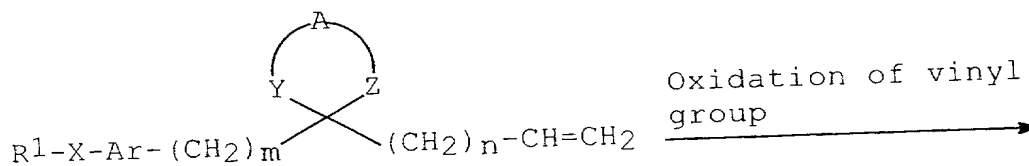


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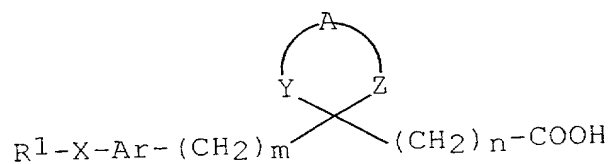


(I-b)
or a salt thereof

Process 2

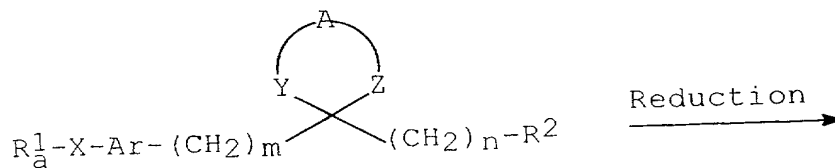


(II)
or a salt thereof



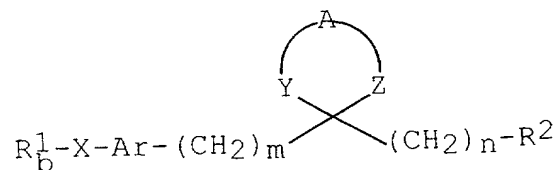
(I-b)
or a salt thereof

Process 3



(I-c)
or a salt thereof

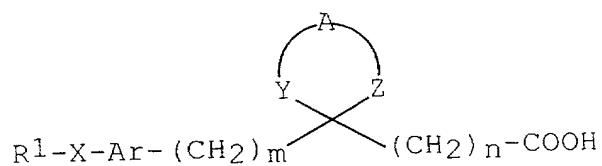
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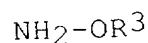
(I-d)
or a salt thereof

10 Process 4

15



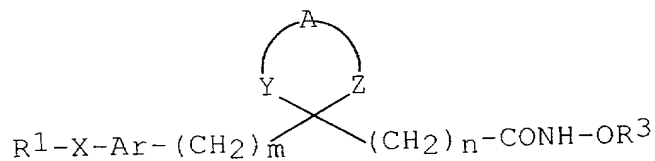
(I-b)
or its reactive derivative
at the carboxy-group,
or a salt thereof



(IV)

or its reactive
derivative at
the amino-group,
or a salt thereof

20

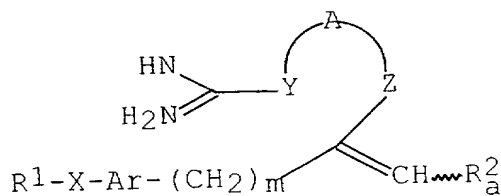


25

(I-e)
or a salt thereof

Process 5

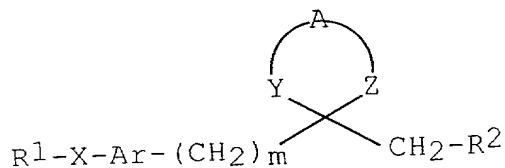
30



(III)
or a salt thereof

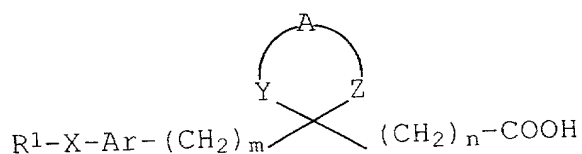
Cyclization

35



(I-f)

or a salt thereof

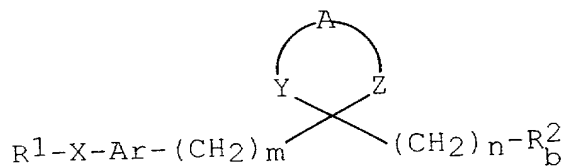
Process 6

(I-b)

or its reactive derivative
at the carboxy-group,
or a salt thereof

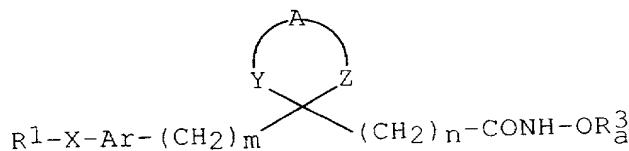
Optically active
amine

or its reactive
derivative at
the amino-group,
or a salt thereof



(I-g)

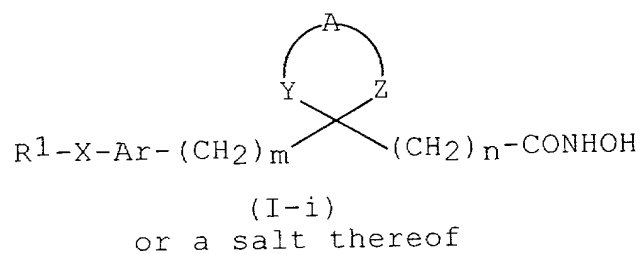
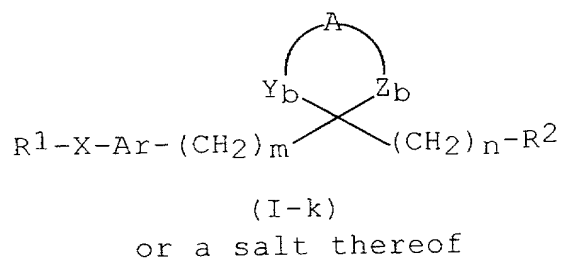
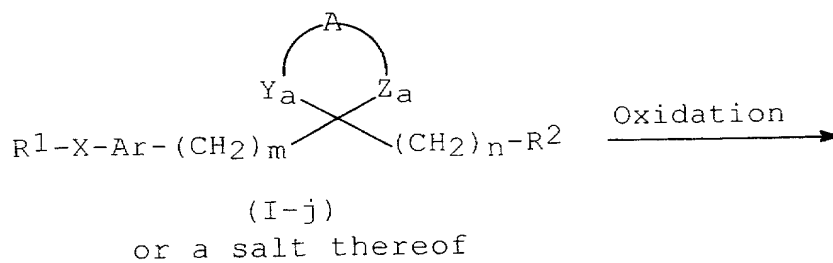
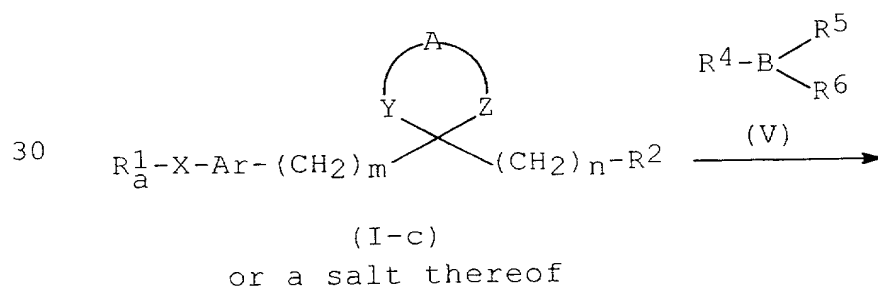
or a salt thereof

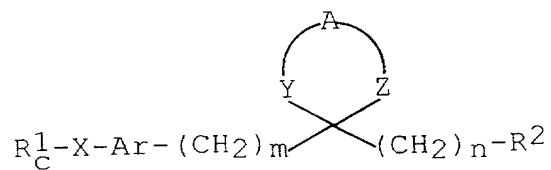
25 Process 7

(I-h)

or a salt thereof

Removal of the
hydroxy-protective group

Process 825 Process 9

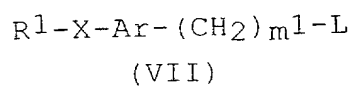
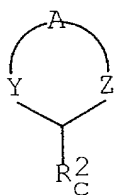


5

(I-~~l~~)
or a salt thereof

Process 10

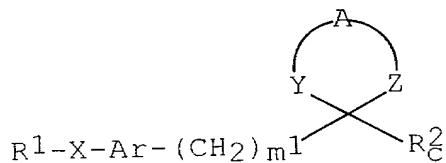
10



or a salt thereof

15

(VI)
or a salt thereof

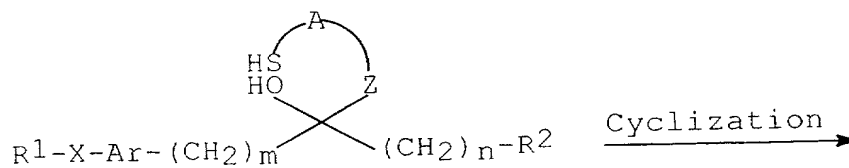


20

(I-m)
or a salt thereof

Process 11

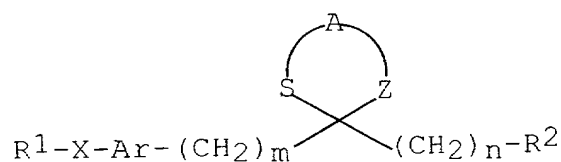
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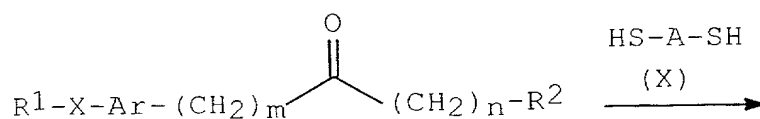
(VIII)
or a salt thereof

35

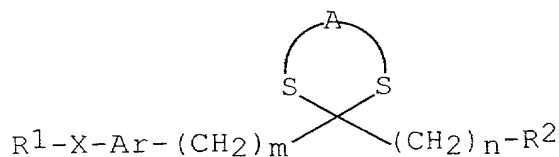


(I-n)
or a salt thereof

Process 12

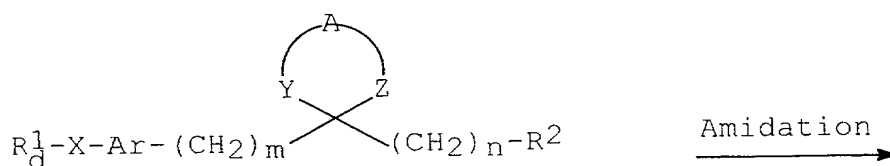


(IX)
or a salt thereof



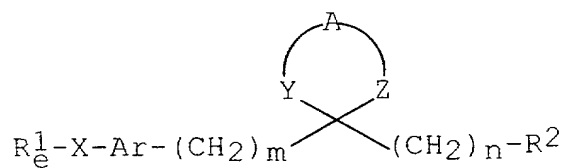
(I-o)
or a salt thereof

Process 13



(I-p)
or its reactive derivative
at the carboxy group,
or a salt thereof

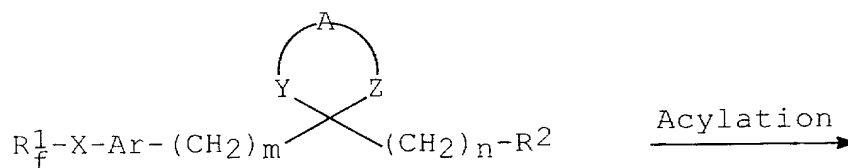
5



(I-q)
or a salt thereof

Process 14

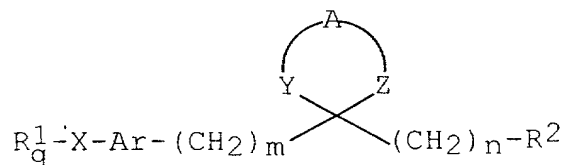
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15

(I-r)
or its reactive derivative
at the amino group,
or a salt thereof

20

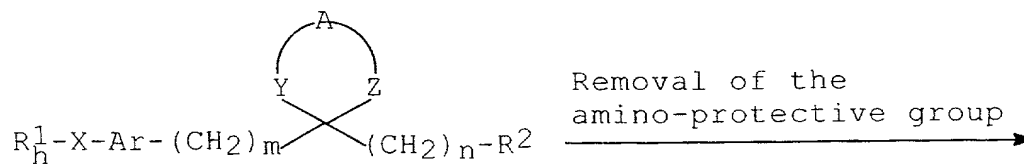


25

(I-s)
or a salt thereof

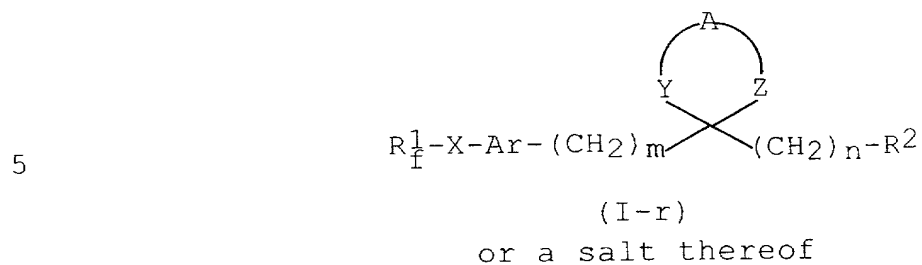
Process 15

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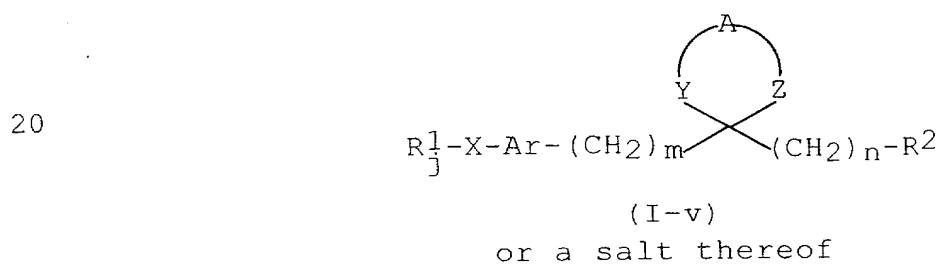
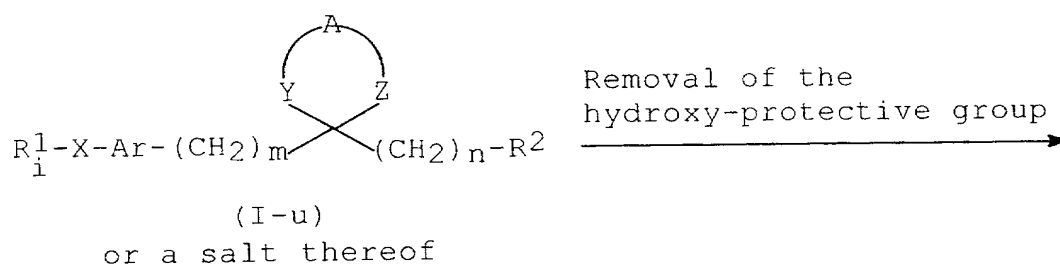
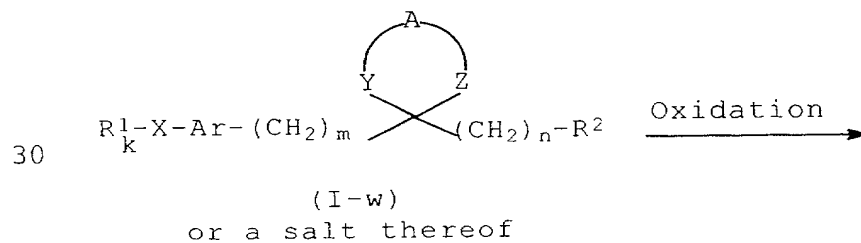


(I-t)
or a salt thereof

35

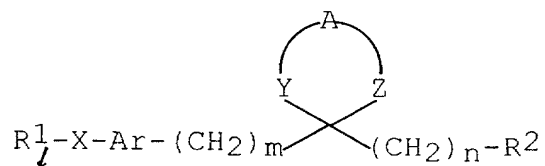
Process 16

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25 Process 17

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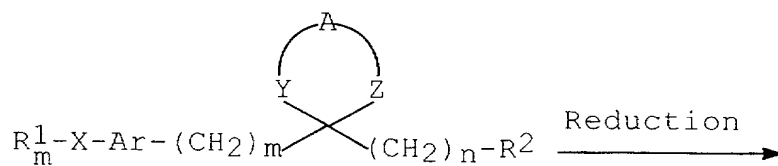
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(I-x)
or a salt thereof

Process 18

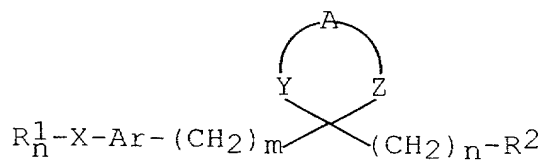
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15

(I-y)
or a salt thereof

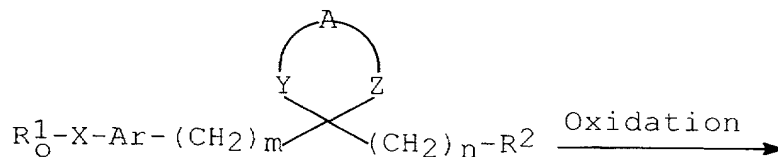
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(I-z)
or a salt thereof

25 Process 19

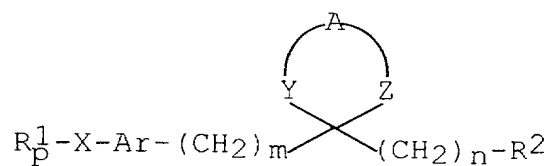
30



(I-aa)
or a salt thereof

35

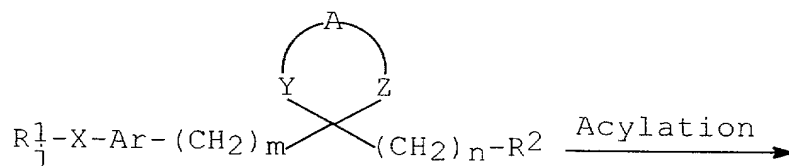
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(I-ab)
or a salt thereof

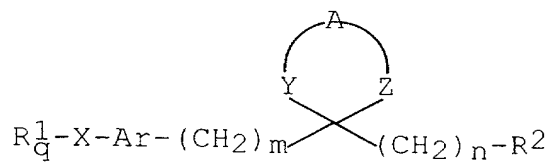
10 Process 20

15



(I-v)
or a salt thereof

20

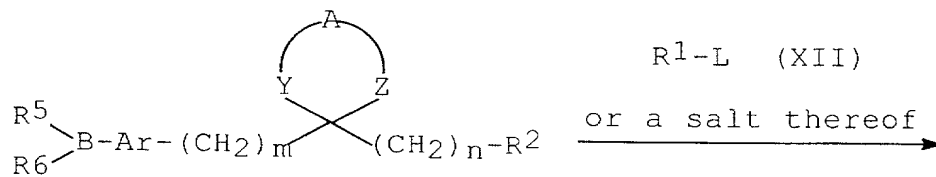


(I-ac)
or a salt thereof

25

Process 21

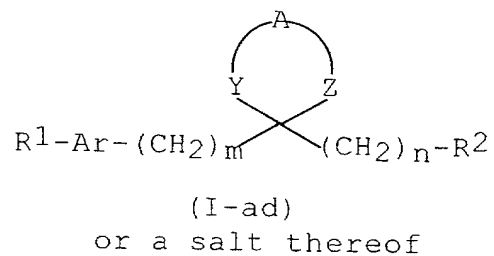
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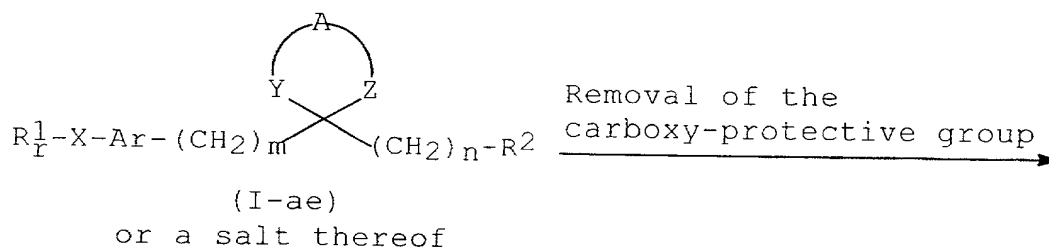
(XI)
or a salt thereof

35

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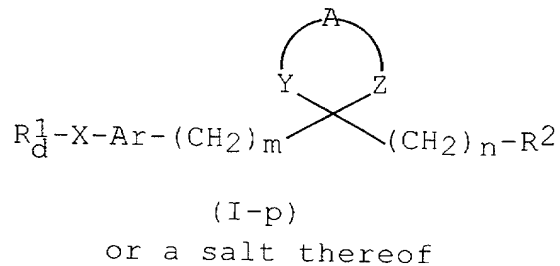
Process 22

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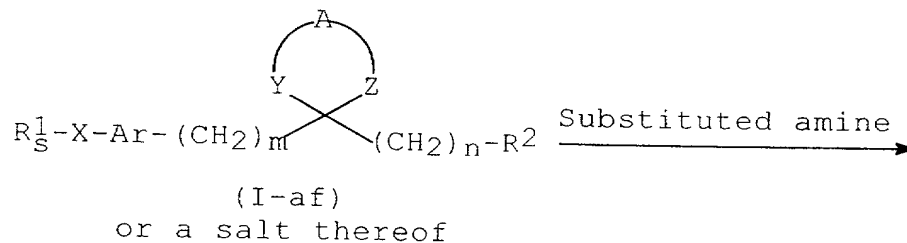
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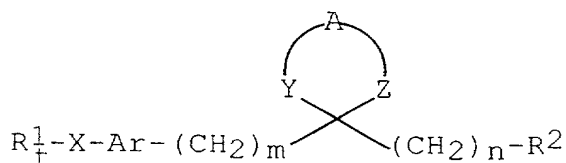
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Process 23

30



35



(I-ag)
or a salt thereof

in which R^1 , R^2 , Ar, A, X, Y, Z, m and n are each as
defined above,

R_a^1 is haloaryl or halo,

R_b^1 is aryl,

R_c^1 is aryl at least substituted by optionally
substituted aryl,

R_d^1 is aryl at least having carboxy moiety,

R_e^1 is aryl at least having amido moiety,

R_f^1 is aryl at least having amino moiety,

R_g^1 is aryl at least having acylamino moiety,

R_h^1 is aryl at least having protected amino moiety,

R_i^1 is aryl at least having protected hydroxy moiety,

R_j^1 is aryl at least having hydroxy moiety,

R_k^1 is aryl at least having thia moiety,

R_l^1 is aryl at least having sulfinyl or sulfonyl
moiety,

R_m^1 is aryl at least having formyl moiety,

R_n^1 is aryl at least having hydroxymethyl moiety,

R_o^1 is aryl at least having vinyl moiety,

R_p^1 is aryl at least having 1,2-dihydroxyethyl
moiety,

R_q^1 is aryl at least having acyloxy moiety,

R_r^1 is aryl at least having protected carboxy moiety,

R_s^1 is aryl at least having halo(lower)alkanoyl
moiety,

R_t^1 is aryl at least having substituted
amino(lower)alkanoyl moiety,

- 5 R_a^2 is protected carboxy,
 R_b^2 is optically active amide,
 R_c^2 is protected carboxy,
 R^3 is hydrogen or hydroxy-protective group,
 R_a^3 is hydroxy-protective group,
 R^4 is optionally substituted aryl,
 R^5 and R^6 are each hydrogen or combined together to
form lower alkylene,
 Y_a is thia, sulfinyl or sulfonyl,
10 Z_a is methylene, thia, sulfinyl or sulfonyl,
provided that at least one of Y_a and Z_a is
thia or sulfinyl,
 Y_b is thia, sulfinyl or sulfonyl,
 Z_b is methylene, thia, sulfinyl or sulfonyl,
15 provided that at least one of Y_b and Z_b is
sulfinyl or sulfonyl,
 L is a leaving group, and
 m^1 is an integer of 1 to 6.

20 The starting compounds used in the above processes can
be prepared according to the following Preparations or by a
conventional method.

Suitable salts of the object compounds (I) to (I-ae)
may be conventional non-toxic pharmaceutically acceptable
25 salts and include an acid addition salt such as an organic
acid salt (e.g., acetate, trifluoroacetate, maleate,
tartrate, fumarate, methanesulfonate, benzenesulfonate,
formate, toluenesulfonate, etc.), an inorganic acid salt
(e.g., hydrochloride, hydrobromide, hydroiodide, sulfate,
30 nitrate, phosphate, etc.), or a salt with a base such as an
amino acid (e.g., arginine, aspartic acid, glutamic acid,
etc.), an alkali metal salt (e.g., sodium salt, potassium
salt, etc.), an alkaline earth metal salt (e.g., calcium
salt, magnesium salt, etc.), an ammonium salt, an organic

base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

The object compounds and pharmaceutically acceptable
5 salts thereof may include solvates such as enclosure compounds (e.g., hydrate, etc.).

Suitable examples and illustrations of the various definitions, which the present invention includes within its scope and which are shown in the above and subsequent
10 descriptions of the present specification, are as follows.

The term "lower" is intended to mean up to 6 carbon atoms, preferably up to 4 carbon atoms, unless otherwise indicated.

Suitable "aryl" and aryl moiety in the term "optionally
15 substituted aryl" may include an aryl having 6 to 10 carbon atoms, such as phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like, preferably phenyl and naphthyl.

Suitable "optionally substituted aryl" may include
20 above-mentioned aryl, which is substituted by the group consisting of the following (A1) to (A35);

- (A1) halogen,
- (A2) lower alkyl,
- (A3) lower alkoxy,
- 25 (A4) halo(lower)alkyl,
- (A5) halo(lower)alkoxy,
- (A6) lower alkenyl,
- (A7) acyl,
- (A8) lower alkylthio, lower alkylsulfinyl, lower
30 alkylsulfonyl,
- (A9) C₆-C₁₀ aryl
- (A10) halo(C₆-C₁₀)aryl,
- (A11) hydroxy,
- (A12) hydroxy(lower)alkyl, protected
35 hydroxy(lower)alkyl,

- (A13) amino,
(A14) carboxy,
(A15) protected carboxy,
(A16) nitro(lower)alkenyl,
5 (A17) lower alkylenedioxy,
(A18) acylamino,
(A19) nitro,
(A20) (C₆-C₁₀)aryl(lower)alkoxy,
(A21) carbamoyl(lower)alkenyl optionally
10 N-substituted by the group consisting of
lower alkyl, C₆-C₁₀ aryl lower alkoxy-
(C₆-C₁₀)aryl, and halo(C₆-C₁₀)aryl,
(A22) lower alkylaminocarbonyloxy,
(A23) lower alkanoyloxy,
15 (A24) lower alkoxy(lower)alkanoyloxy,
(A25) lower alkoxycarbonyloxy,
(A26) lower alkenoyloxy optionally substituted by
heterocyclic group of the above (1) to (14),
(A27) lower cycloalkanecarbonyloxy,
20 (A28) lower alkoxy substituted by the group
consisting of carboxy, protected carboxy,
lower alkanoyl, lower cycloalkanecarbamoyl,
and lower alkylcarbamoyl,
(A29) lower alkylcarbamoyloxy(lower)alkyl,
25 (A30) lower alkoxycarbonylamino(lower)alkyl,
(A31) amino(lower)alkyl,
(A32) lower alkylcarbamoyl(lower)alkyl,
(A33) heterocyclic-carbonylamino, the heterocyclic
30 group being selected from the above (1) to
(14) and optionally being substituted N-
protective group,
(A34) the above heterocyclic groups (1) to (14)
being optionally substituted by lower alkyl,
and
35 (A35) oxo.

Suitable "heterocyclic group" in the term "optionally substituted heterocyclic group" means saturated or unsaturated, monocyclic or polycyclic heterocyclic group
5 containing at least one hetero atom such as oxygen atom, sulfur atom, nitrogen atom and the like.

Preferable heterocyclic groups are following (1) to (14):

- 10 (1) unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms
(pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl,
15 pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), and the like);
20 (2) saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms
(azetidiny, pyrrolidinyl, imidazolidinyl, piperidinyl, piperidino, pyrazolidinyl, piperazinyl, and the like);
25 (3) unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms
(thienyl, and the like);
30 (4) unsaturated condensed (preferably bicyclic) 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 to 5 nitrogen atoms
35 (indolyl, isoindolyl, indolizinyl, benzimidazolyl,

quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, and the like);

5 (5) unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms

(furyl, and the like);

10 (6) saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms

(oxolanyl, and the like);

15 (7) unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms

(oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), and the like);

20 (8) unsaturated condensed (preferably bicyclic) 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 oxygen atoms

(benzofuranyl, benzodihydrofuranyl, benzodioxolenyl, and the like);

25 (9) unsaturated condensed (preferably bicyclic) 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 sulfur atoms (benzothienyl, dihydrobenzothienyl, and the like);

30 (10) saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms

(morpholinyl, morpholino, and the like);

35 (11) unsaturated condensed (preferably bicyclic) 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 oxygen atoms

and 1 to 3 nitrogen atoms

(benzoxazolyl, benzoxadiazolyl, and the like);

(12) unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms

(thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.), and the like);

(13) saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms (thiazolidinyl, and the like);

(14) unsaturated condensed (preferably bicyclic) 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms (benzothiazolyl, benzothiadiazolyl, and the like);

etc.

These heterocyclic groups may have one or more substituents. Examples of the substituents for substituted heterocyclic group may be the same as those for "optionally substituted aryl" (above-mentioned (A1) to (A35))

Suitable "lower alkyl" may include a straight or branched alkyl having 1 to 6 carbon atoms, and exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and the like, and the most preferably methyl for R¹.

Suitable "lower alkenyl" may include a straight or branched alkenyl having 2 to 6 carbon atoms, and exemplified by ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl and the like.

Suitable "lower alkoxy" may include a straight or branched alkenyl having 1 to 6 carbon atoms, and exemplified

by methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, hexyloxy and the like.

Suitable "hydroxy-protective group" may include a
5 conventional protective group, for example, substituted
lower alkyl such as lower alkoxy(lower)alkyl (e.g.,
methoxymethyl), lower alkoxy(lower)alkoxy(lower)alkyl (e.g.,
methoxyethoxymethyl) and substituted or unsubstituted
aryl(lower)alkyl (e.g., benzyl nitrobenzyl); acyl such as
10 lower alkanoyl (e.g., acetyl, propionyl, pivaloyl), aroyl
(e.g., benzoyl, fluorene-carbonyl), lower alkoxycarbonyl
(e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,
isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-
butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl),
15 substituted or unsubstituted aryl(lower)alkoxycarbonyl (e.g.,
benzyloxycarbonyl, bromobenzyloxycarbonyl), arenesulfonyl
(e.g., benzenesulfonyl, tosyl) and alkanesulfonyl (e.g.,
methanesulfonyl, ethanesulfonyl); tri(lower)alkylsilyl (e.g.,
trimethylsilyl); tetrahydropyranyl; and the like, preferably
20 tetrahydropyranyl.

Suitable "halogen" includes fluorine, bromine, chlorine and iodine.

Suitable acyl and acyl moiety of "acylamino" includes
acyl such as aliphatic acyl, aromatic acyl, heterocyclic
25 acyl and aliphatic acyl substituted by aromatic or
heterocyclic group(s) derived from carboxylic, carbonic,
sulfonic and carbamic acids.

The aliphatic acyl includes saturated or unsaturated,
acyclic or cyclic ones, for example, alkanoyl such as lower
30 alkanoyl (e.g., formyl, acetyl, propionyl, butyl, isobutyl,
valeryl, isovaleryl, pivaloyl, hexanoyl, etc.),
alkylsulfonyl such as lower alkylsulfonyl (e.g., mesyl,
ethylsulfonyl, propylsulfonyl, isopropylsulfonyl,
butylsulfonyl, isobutylsulfonyl, pentylsulfonyl,
35 hexylsulfonyl, etc.), carbamoyl, N-alkylcarbamoyl (e.g.,

methylearbamoyl, ethylearbamoyl, etc.), alkoylearbonyl sueh
as lower alkoylearbonyl (e.g., methoylearbonyl,
ethoylearbonyl, propoylearbonyl, butoylearbonyl, tert-
butoylearbonyl, etc.), alkenyloylearbonyl sueh as lower
5 alkenyloylearbonyl (e.g., vinyloylearbonyl, allyloylearbonyl,
etc.), alkenoyl sueh as lower alkenoyl (e.g., aeuryloyl,
methaeuryloyl, euronoyl, etc.), eyleoalkaneearbonyl sueh as
eyleo(lower)alkaneearbonyl (e.g., eyleopropaneearbonyl,
eyleopentaneearbonyl, eyleohexaneearbonyl, etc.), and the
10 like.

The aromatic aeyl may include C₆-C₁₀ aroyl (e.g.,
benzoyl, toluoyl, xyloyl, etc.), N-(C₆-C₁₀)arylearbamoyl
(e.g., N-phenylearbamoyl, N-tolylearbamoyl,
N-naphthylearbamoyl, etc.), C₆-C₁₀ arenesulfonyl (e.g.,
15 benzenesulfonyl, tosyl, etc.), and the like.

The heteroeyclic aeyl may include heteroeyclic-earbonyl
(e.g., furoyl, thenoyl, nieotinoyl, isonieotinoyl,
thiazolylearbonyl, thiadiazolylearbonyl, tetrazolylearbonyl,
etc.), and the like.

20 The aliphatic aeyl substituted by aromatic group(s) may
include aralkanoyl sueh as phenyl(lower)alkanoyl (e.g.,
phenylaeetyl, phenylpropionyl, phenylhexanoyl, etc.),
aralkoylearbonyl sueh as phenyl(lower)alkoylearbonyl (e.g.,
benzyloylearbonyl, phenethyloylearbonyl, etc.),
25 aryloxyalkanoyl sueh as phenoxy(lower)alkanoyl (e.g.,
phenoxyaeetyl, phenoxypropionyl, etc.), and the like.

The aliphatic aeyl substituted by heteroeyclic group(s)
may include heteroeyclic-alkanoyl sueh as heteroeyclic-
(lower)alkanoyl (e.g., thienylaeetyl, imidazolylaeetyl,
30 furylaeetyl, tetrazolylaeetyl, thiazolylaeetyl,
thiadiazolylaeetyl, thienylpropionyl, thiadiazolylpropionyl,
etc.), and the like.

These aeyl groups may be further substituted by one or
more suitable substituents as those for "optionally
35 substituted aryl" (above-mentioned (A1) to (A35)).

Suitable "protected carboxy" includes esterified carboxy wherein "esterified carboxy" is as defined below.

Suitable examples of the ester moiety of the esterified carboxy are lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, etc.) and the like, which may have at least one suitable substituent. Examples of the substituted lower alkyl ester are lower alkanoyloxy(lower)alkyl ester [e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-(or 2-)acetoxylethyl ester, 1-(or 2- or 3-)acetoxypentyl ester, 1-(or 2- or 3- or 4-)acetoxylhexyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(or 2- or 3-)propionyloxypropyl ester, 1-(or 2-)butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1-(or 2-)pentanoyloxyethyl ester, etc.], lower alkanesulfonyl(lower)alkyl ester (e.g., 2-mesyloethyl ester, etc.), mono(or di or tri)halo(lower)alkyl ester (e.g., 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.); lower alkoxycarbonyloxy(lower)alkyl ester [e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, tert-butoxycarbonyloxymethyl ester, 1-(or 2-)methoxycarbonyloxyethyl ester, 1-(or 2-)ethoxycarbonyloxyethyl ester, 1-(or 2-)isopropoxycarbonyloxyethyl ester, etc.], phthalidylidene(lower)alkyl ester, (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.]; lower alkenyl ester (e.g., vinyl ester, allyl ester,

etc.); lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.); ar(lower)alkyl ester which may have at least one suitable substituent (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.); aryl ester which may have at least one suitable substituent (e.g., phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like.

More preferable example of the protected carboxy thus defined may be C₁-C₄ alkoxy carbonyl, and the most preferable one may be methoxycarbonyl, ethoxycarbonyl, and t-butoxycarbonyl for R².

Said "amidated carboxy" can be referred to the ones as mentioned below.

Suitable examples of the amidated carboxy may include optionally substituted carbamoyl such as

- carbamoyl,
- N-hydroxycarbamoyl,
- N-(protected hydroxy)carbamoyl, wherein said hydroxy-protective group may be the same as mentioned above (e.g. tetrahydropyranyl, etc.),
- mono(or di)(lower)alkylcarbamoyl wherein the lower alkyl group may be the same as those mentioned above (e.g. methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, 3-methylbutylcarbamoyl, isobutylcarbamoyl, pentylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, etc.),
- N-(aryl(lower)alkyl)carbamoyl such as phenyl(lower)-alkylcarbamoyl (e.g. 1-phenylethylcarbamoyl, (R)-(+)-1-phenylethyl, etc.),
- cyclo(C₃-C₇)alkylcarbamoyl (e.g. cyclohexylcarbamoyl, etc.),

-carbamoyl substituted by amino or di(lower)alkylamino [e.g. N-aminocarbamoyl, N-(dimethylamino)carbamoyl, etc.],
-lower alkyleneaminocarbonyl (e.g. pyrrolidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, etc.),

5 said alkylene being optionally substituted by
 carboxy or protected carboxy as mentioned
 above such as lower alkoxycarbonyl [e.g. carboxypyrrolidin-1-ylcarbonyl,
 (methoxycarbonyl)pyrrolidin-1-ylcarbonyl,
10 (ethoxycarbonyl)pyrrolidin-1-ylcarbonyl,
 etc.],

 or said lower alkylene being optionally
 interrupted by other hetero atom(s) such as
 nitrogen, oxygen or sulfur (e.g.
15 morpholinocarbonyl, etc.),
-lower alkylsulfonylcarbamoyl (e.g. methylsulfonylcarbamoyl,
 etc.),
-arenesulfonylcarbamoyl (e.g. benzenesulfonylcarbamoyl,
 etc.), and the like.

20 Preferable example of the amidated carboxy thus defined
may be :

N-hydroxycarbamoyl, N-tetrahydropyranyloxy carbamoyl, and
N-(phenylethyl)carbamoyl for R².

25 Suitable "leaving group" may include halogen as
mentioned above, acyloxy such as sulfonyloxy (e.g., mesyloxy,
tosyloxy, etc.), alkoxy (e.g., tert-butoxy, etc.), aralkoxy
(e.g., benzyloxy, etc.), and the like, preferably halogen
30 and the most preferably bromine.

 Suitable "lower alkylene" may include straight or
branched one such as methylene, ethylene, trimethylene,
35 propylene, tetramethylene, ethylethylene, pentamethylene,

hexamethylene, and the like, in which more preferable one may be C₁-C₄ alkylene, and the most preferable one may be ethylene, 1-methyltrimethylene, and trimethylene.

5 Suitable "halo(lower)alkyl" may be above-mentioned lower alkyl substituted by halogen as mentioned above, in which more preferable one may be halo(C₁-C₄)alkyl.

10 Suitable "halo(lower)alkoxy" may be above-mentioned lower alkoxy substituted by halogen as mentioned above, in which more preferable one may be halo(C₁-C₄)alkoxy.

15 Suitable "lower alkylthio" may be thio group substituted by above-mentioned lower alkyl, in which more preferable one may be C₁-C₄ alkylthio (e.g. methylthio, ethylthio, etc.).

20 Suitable "lower alkylsulfinyl" may include methylsulfinyl, ethylsulfinyl, and the like, in which more preferable one may be C₁-C₄ alkylsulfinyl (e.g. methylsulfinyl, etc.).

25 Suitable "lower alkylsulfonyl" may include methylsulfonyl, ethylsulfonyl, and the like, in which more preferable one may be C₁-C₄ alkylsulfonyl (e.g. methylsulfonyl, etc.).

30 Suitable "haloaryl" may be aforementioned aryl substituted by halogen as mentioned above, in which more preferable one may be halo(C₆-C₁₀)aryl, and the most preferable one may be 4-fluorophenyl.

35 Suitable "hydroxy(lower)alkyl" may be above-mentioned lower alkyl substituted by hydroxy as mentioned above, in which more preferable one may be hydroxy(C₁-C₄)alkyl.

Suitable "protected hydroxy(lower)alkyl" may be above-mentioned hydroxy(lower)alkyl group protected by a conventional hydroxy-protective group such as acyl, (lower
5 alkyl)(diaryl)silyl group (e.g. (t-butyl)(diphenyl)silyl, etc.), and the like.

Suitable "aryl(lower)alkoxy" may include benzyloxy, phenylethoxy, and the like, in which more preferable one may
10 be phenyl(C₁-C₄)alkoxy (e.g. benzyloxy, etc.).

Suitable "carbamoyl(lower)alkenyl" may include carbamoylethenyl, carbamoylallyl, and the like, in which more preferable one may be carbamoyl(C₂-C₄)alkenyl (e.g.
15 carbamoylethenyl, etc.).

Suitable "lower alkoxyaryl" may include methoxyphenyl, ethoxyphenyl, and the like, in which more preferable one may be C₁-C₄ alkoxyphenyl (e.g. methoxyphenyl, etc.).
20

Preferable examples of "carbamoyl(lower)alkenyl optionally N-substituted by the group consisting of lower alkyl, aryl, lower alkoxyaryl and haloaryl" may include lower alkylcarbamoyl(lower)alkenyl (e.g. carbamoylethenyl,
25 methylcarbamoylethenyl, ethylcarbamoylethenyl, propylcarbamoylethenyl, isopropylcarbamoylethenyl, dimethylcarbamoylethenyl, etc.), C₆-C₁₀ arylcarbamoyl(lower)alkenyl (e.g. phenylcarbamoylethenyl, etc.), lower alkoxy(C₆-C₁₀)arylcarbamoyl(lower)alkenyl (e.g.
30 methoxyphenylcarbamoylethenyl, etc.), haloarylcarbamoyl(lower)alkenyl (e.g. fluorophenylcarbamoylethenyl, etc.), and the like.

Suitable "lower alkylaminocarbonyloxy" may include
35 methylaminocarbonyloxy, ethylaminocarbonyloxy, and the like,

in which more preferable one may be C₁-C₄ alkylaminocarbonyloxy (e.g. methylaminocarbonyloxy, ethylaminocarbonyloxy, etc.).

5 Suitable "lower alkanoyloxy" may include acetyoxy, propanoyloxy, and the like, in which more preferable one may be C₁-C₄ alkanoyloxy (e.g. propanoyloxy, etc.).

10 Suitable "lower alkoxy(lower)alkanoyloxy" may include methoxyacetyloxy, ethoxyacetyloxy, and the like, in which more preferable one may be C₁-C₄ alkoxy(C₁-C₄)alkanoyloxy (e.g. methoxyacetyloxy, etc.).

15 Suitable "lower alkoxy carbonyloxy" may include methoxycarbonyloxy, ethoxycarbonyloxy, and the like, in which more preferable one may be C₁-C₄ alkoxy carbonyloxy (e.g. ethoxycarbonyloxy, etc.).

20 Suitable "lower alkenoyloxy" may include acryloyloxy, and the like, in which more preferable one may be C₂-C₄ alkenoyloxy (e.g. acryloyloxy, etc.).

25 Preferable examples of "lower alkenoyloxy optionally substituted by heterocyclic group" may include lower alkenoyloxy optionally substituted by the above-mentioned heterocyclic group (1) (e.g. pyridyl, etc.) such as pyridylacryloyloxy, and the like.

30 Suitable "lower cycloalkanecarbonyloxy" may include C₃-C₇ cycloalkanecarbonyloxy such as cyclopropanecarbonyloxy, cyclobutanecarbonyloxy, and the like, in which more preferable one may be C₄-C₆ alkanecarbonyloxy (e.g. cyclopropanecarbonyloxy, etc.).

35 Suitable "lower cycloalkanecarbamoyl" may include C₃-C₇

cycloalkanecarbamoyl such as cyclopropanecarbamoyl, cyclobutanecarbamoyl, and the like, in which more preferable one may be C₄-C₆ cycloalkanecarbamoyl (e.g. cyclopropanecarbamoyl, etc.).

5

Suitable "lower alkylcarbamoyl" may include methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl and the like, in which more preferable one may be C₁-C₄ alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, etc.).

10

Preferable examples of "lower alkoxy substituted by the group consisting of carboxy, protected carboxy, lower alkanoyl, lower cycloalkanecarbamoyl, lower alkylcarbamoyl may include arboxy(lower)alkoxy (e.g. carboxymethoxy, etc.), lower alkoxycarbonyl(lower)alkoxy (e.g. ethoxycarbonylmethoxy, butoxycarbonylmethoxy, etc.), lower alkanoyl(lower)alkoxy (e.g. propanoylmethoxy, etc.), lower cycloalkanecarbamoyl(lower)alkoxy (e.g. cyclopropylcarbamoylmethoxy, etc.), loweralkylcarbamoyl(lower)alkoxy (e.g. methylcarbamoylmethoxy, ethylcarbamoylmethoxy, propylcarbamoylmethoxy, etc.), and the like.

25

Suitable "lower alkylcarbamoyloxy(lower)alkyl" may include methylcarbamoyloxymethyl, ethylcarbamoyloxymethyl, and the like, in which more preferable one may be C₁-C₄ alkylcarbamoyloxy(C₁-C₄)alkyl (e.g. methylcarbamoyloxymethyl, etc.).

30

Suitable "lower alkoxycarbonylamino(lower)alkyl" may include methoxycarbonylaminomethyl, t-butoxycarbonylaminomethyl, and the like, in which more preferable one may be C₁-C₄ alkoxycarbonylamino(C₁-C₄)alkyl (e.g. methoxycarbonylaminomethyl,

35

t-butoxycarbonylaminomethyl, etc.).

Suitable "amino(lower)alkyl" may include aminomethyl, aminoethyl, and the like, in which more preferable one may
5 be amino(C₁-C₄)alkyl (e.g. aminomethyl, etc.).

Suitable "lower alkylcarbamoyl(lower)alkyl" may include methylcarbamoylmethyl, methylcarbamoylethyl, ethylcarbamoylmethyl, ethylcarbamoylethyl, and the like, in
10 which more preferable one may be C₁-C₄ alkylcarbamoyl-(C₁-C₄)alkyl (e.g. methylcarbamoylmethyl, etc.).

Suitable "heterocyclic-carbonylamino" may include carbonylamino group substituted by the above-mentioned
15 heterocyclic group (2), (4) and (5) (e.g. pyrrolidinyl, teretahydroisoquinolyl, furyl, etc.) such as pyrrolidinylcarbonylamino, 1,2,3,4-teretahydroisoquinolylcarbonylamino, furylcarbonylamino, and the like.

20 Preferable examples of "optionally substituted heterocyclic-carbonylamino" may include above-mentioned heterocyclic-carbonylamino optionally the heterocyclic group being substituted by N-protective group (e.g. acyl such as
25 alkoxy carbonyl, etc.) such as pyrrolidinylcarbonylamino, 1,2,3,4-teretahydroisoquinolylcarbonylamino, (N-(t-butoxycarbonyl)-1,2,3,4-teretahydroisoquinolyl)-carbonylamino, furylcarbonylamino, and the like.

30 Suitable "nitro(lower)alkenyl" may be above-mentioned lower alkenyl substituted by nitro, in which more preferable one may be nitro(C₂-C₄)alkenyl.

Suitable "lower alkylenedioxy" may include straight or
35 branched one such as methylenedioxy, ethylenedioxy,

trimethylenedioxy, propylenedioxy, tetramethylenedioxy, ethylethylenedioxy, pentamethylenedioxy, hexamethylenedioxy, and the like, in which more preferable one may be C₁-C₄ alkylenedioxy.

5

Suitable "amido" may be the same as those for "amidated carboxy", and preferably lower alkylcarbamoyl, and the most preferably methylcarbamoyl.

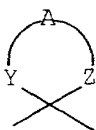
10 Suitable "acylamino" may be amino substituted by acyl as mentioned above.

Suitable "substituted amine" may include amino group substituted by the above-mentioned substituent (A2) to (A12),
15 (A14) to (A17), (A20) to (A32) and (A34).

Preferable examples may be hydroxy (lower)alkylamine (e.g. hydroxyethylamine, etc.), above-mentioned N-containing heterocyclic group (e.g. morpholino, etc.), lower
20 alkenylamine (e.g. allylamine, etc.), C₆-C₁₀ aryl(lower)alkylamine e.g. benzylamine, etc.), lower alkylamine (e.g. t-butylamine, pentylamine, etc.), heterocyclic(lower)alkylamine such as pyridyl(lower)alkylamine (e.g. pyridylmethylamine, etc.),
25 lower alkoxy(lower)alkylamine (e.g. ethoxyethylamine, etc.), and the like.

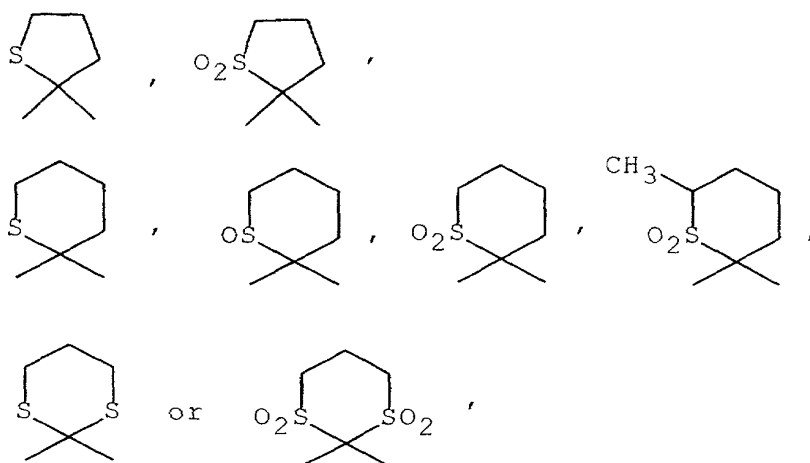
Preferable examples of the formula:

30



is one of the following formulae:

35



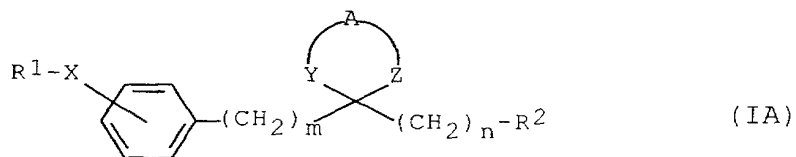
and the like.

In the object compounds (I),

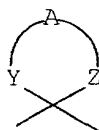
- 15 (i) the preferred one may be the compounds (I) wherein m and n are each 0 or 1, and
- (ii) the more preferred one may be the compounds of the above item (i) wherein A is ethylene, 1-methyltrimethylene, or trimethylene.

The more preferred object compounds (I) are:

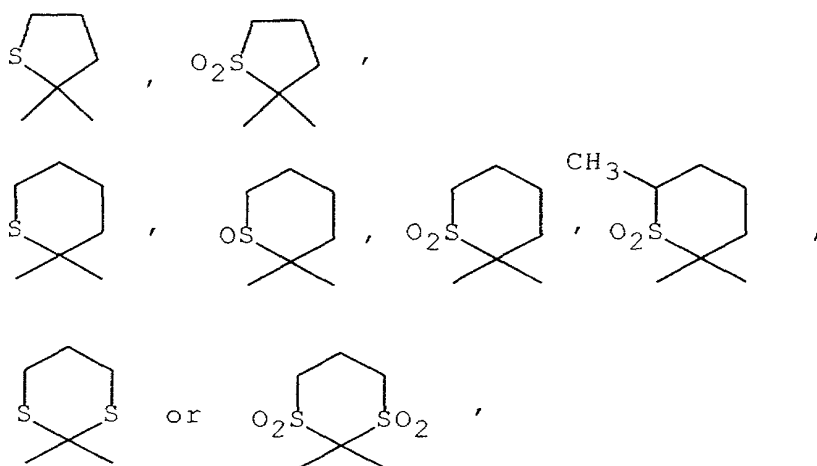
- (iii) The compounds (I), having the following formula:



30 wherein a group of the formula:



35 is one of the following formulae:

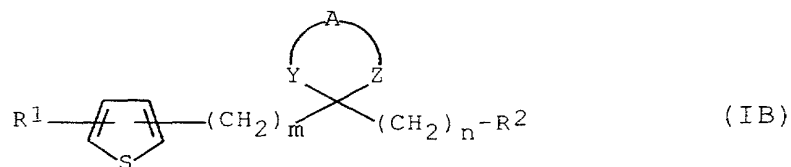


R¹ is lower alkyl, phenyl, halophenyl, or (halo)(phenyl)phenyl,

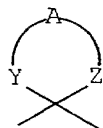
R² is carboxy or hydroxyaminocarbonyl, and

m and n are each an integer of 0 or 1, and $m+n=1$.

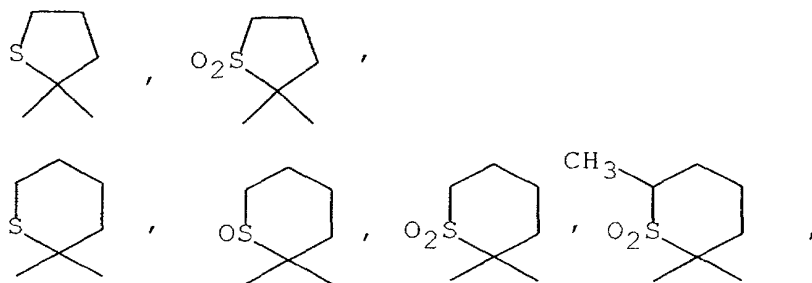
(iv) The compounds (I), having the following formula:

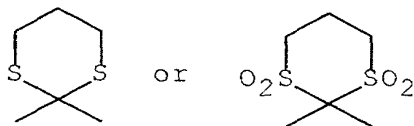


wherein a group of the formula:



is one of the following formulae:





5

R^2 is carboxy or hydroxyaminocarbonyl,

m and n are each an integer of 0 or 1, and $m+n=1$,

R^1 is halogen; heterocyclic group consisting of

pyridyl, thienyl, furyl, benzofuranyl or

10

benzothienyl, wherein the heterocyclic group is

optionally substituted by the group consisting of

lower alkanoyl, lower alkyl, lower alkoxy, lower

alkoxycarbonylamino and lower alkylcarbamoyl;

naphtyl or phenyl optionally substituted by the

15

group consisting of the following (C1) to (C31);

(C1) halogen,

(C2) lower alkyl,

(C3) lower alkoxy,

(C4) halo(lower)alkyl,

20

(C5) halo(lower)alkoxy,

(C6) lower alkenyl,

(C7) lower alkylcarbamoyl, carbamoyl,

phenyl(lower)alkylcarbamoyl, lower alkanoyl,

(C8) lower alkylthio, lower alkylsulfinyl, lower

25

alkylsulfonyl,

(C9) phenyl, naphthyl,

(C10) halophenyl,

(C11) hydroxy,

(C12) mono- or dihydroxy(lower)alkyl,

30

phenoxycarbonyloxy(lower)alkyl

(C13) amino,

(C14) carboxy,

(C15) lower alkylenedioxy,

(C16) lower alkanoylamino,

35

phenyl(lower)alkanoylamino,

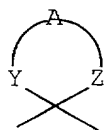
halophenyl(lower)alkanoylamino, lower
alkoxy(lower)alkanoylamino, lower
alkoxy(lower)alkanoylamino,
phenoxy(lower)alkanoylamino, lower
5 alkoxyphenoxy(lower)alkanoylamino, lower
alkylphenoxy(lower)alkanoylamino,
halophenoxy(lower)alkanoylamino,
carboxy(lower)alkanoylamino, lower
alkoxycarbonyl(lower)alkanoylamino,
10 lower alkylcarbamoyl(lower)alkanoylamino,
halo(lower)alkanoylamino,
lower alkenyl(lower)alkanoylamino,
lower alkoxy(lower)alkanoylamino,
phenyl(lower)alkoxy(lower)alkanoylamino,
15 piperidinyloxy(lower)alkanoylamino, N-lower
alkoxycarbonylpiperidinyloxy-
(lower)alkanoylamino, pyridyloxy(lower)-
alkanoylamino,
hydroxy(lower)alkanoylamino,
20 lower alkanoyloxy(lower)alkanoylamino,
lower alkylcarbamoyloxy(lower)alkanoylamino,
N,N-di(lower alkyl)carbamoyloxy,
piperidino-carbonyloxy(lower)alkanoylamino,
phenyl(lower)alkylcarbamoyloxy(lower)-
25 alkanoylamino,
lower alkoxycarbonylamino(lower)alkanoylamino,
amino(lower)alkanoylamino, lower
alkoxycarbonylamino(lower)alkanoylamino,
fluorenylmethoxycarbonylamino(lower)-
30 alkanoylamino, lower
alkylamino(lower)alkanoylamino, [N,N-di(lower
alkyl)amino](lower)alkanoylamino,
[N-lower alkyl-N-(lower
alkoxycarbonyl)amino](lower)alkanoylamino,
35 [N-lower alkyl-N-(fluorenylmethoxycarbonyl)-

amino] (lower) alkanoylamino,
[N-lower alkyl-N-(mono- or di(lower)-
alkylcarbamoyl)amino] (lower) alkanoylamino,
[N-(mono- or di(lower alkyl)carbamoyl)-
5 amino] (lower) alkanoylamino,
benzoylamino (lower) alkanoylamino,
lower alkanoylamino (lower) alkanoylamino,
lower alkanesulfonylamino (lower) alkanoylamino,
lower alkoxy (lower) alkanoylamino-
10 (lower) alkanoylamino,
cyclo (lower) alkyloxycarbonylamino-
(lower) alkanoylamino,
pyridylcarbonylamino (lower) alkanoylamino,
morpholinocarbonylamino (lower) alkanoylamino,
15 phenyl (lower) alkoxycarbonylamino-
(lower) alkanoylamino,
lower alkoxyphenylsulfonylamino-
(lower) alkanoylamino,
hydroxy (lower) alkylamino (lower) alkanoylamino,
20 morpholino (lower) alkanoylamino,
oxooxazolidinyl (lower) alkanoylamino,
oxopyrrolidinyl (lower) alkanoylamino,
trimethylhydantoinyl (lower) alkanoylamino,
lower alkenylamino (lower) alkanoylamino,
25 lower alkoxy (lower) alkylamino (lower)-
alkanoylamino,
phenyl (lower) alkylamino (lower) alkanoylamino,
pyridyl (lower) alkylamino (lower) alkanoylamino,
lower alkoxycarbonylamino,
30 phenyl (lower) alkoxycarbonylamino,
lower alkoxy (lower) alkoxycarbonylamino,
halo (lower) alkoxycarbonylamino,
amino (lower) alkoxycarbonylamino,
phthalimido (lower) alkoxycarbonylamino,
35 carbamoylamino,

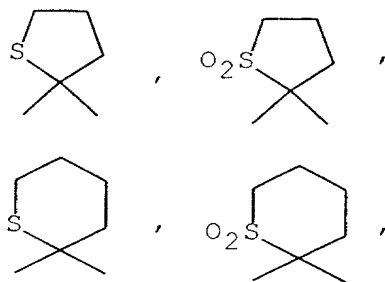
(mono- or di(lower alkyl)carbamoylamino,
naphthylcarbamoylamino,
halophenylcarbamoylamino,
lower alkoxyphenylcarbamoylamino,
5 lower alkenylcarbamoylamino,
cyclo(lower)alkyl(lower)alkylcarbamoylamino,
phenyl(lower)alkylcarbamoylamino,
halo(lower)alkylcarbamoylamino,
lower alkoxy(lower)alkylcarbamoylamino,
10 hydroxy(lower)alkylcarbamoylamino, (lower
alkyl)(diphenyl)silyloxy(lower)alkyl-
carbamoylamino,
carboxy(lower)alkylcarbamoylamino, lower
alkoxycarbonyl(lower)alkylcarbamoylamino,
15 lower alkylcarbamoyl(lower)alkyl-
carbamoylamino, or
pyridylcarbamoylamino,
lower alkylsulfonylamino,
lower alkenoylamino,
20 lower cycloalkanecarbonylamino,
lower alkenyloxycarbonylamino,
phenoxycarbonylamino,
lower alkylthiocarbonylamino,
(C17) phenyl(lower)alkoxy,
25 (C18) lower alkenyl, mono- or di(lower
alkyl)carbamoyl(lower)alkenyl, (2-
(methylcarbamoyl)ethenyl, 2-
(ethylcarbamoyl)ethenyl, 2-
(propylcarbamoyl)ethenyl, 2-
30 (isopropylcarbamoyl)ethenyl, 2-
(dimethylcarbamoyl)ethenyl,)
phenylcarbamoyl(lower)alkenyl,
lower alkoxy-carbamoyl(lower)alkenyl,
halophenylcarbamoyl(lower)alkenyl,
35 (C19) lower alkylaminocarbonyloxy,

- (C20) lower alkanoyloxy,
 (C21) lower alkoxy(lower)alkanoyloxy,
 (C22) lower alkoxycarbonyloxy,
 (C23) pyridyl(lower)alkenoyloxy
 5 (C24) lower cycloalkanecarbonyloxy,
 (C25) carboxy(lower)alkoxy,
 lower alkoxycarbonyl(lower)alkoxy,
 lower alkanoyl(lower)alkoxy,
 lower cycloalkanecarbamoyl(lower)alkoxy,
 10 lower alkylcarbamoyl(lower)alkoxy,
 (C26) lower alkylcarbamoyloxy(lower)alkyl,
 (C27) lower alkoxycarbonylamino(lower)alkyl,
 (C28) amino(lower)alkyl,
 (C29) lower alkylcarbamoyl(lower)alkyl,
 15 (C30) furylcarbonylamino,
 teretahydroisoquinolylcarbonylamino, N-lower
 alkoxycarbonyl-
 teretahydroisoquinolylcarbonylamino,
 pyrrolidinylcarbonylamino,
 20 (C31) oxazolyl, lower alkyloxadiazolyl.

(V) The compounds (I) of the above (iv), in which
 a group of the formula:

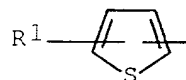


is one of the following formulae:



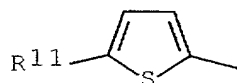
R^2 is hydroxyaminocarbonyl,
m is 0 and n is 1,

a group of the formula:



is one of the group of the following formulae (a) to
(e);

(a)



wherein

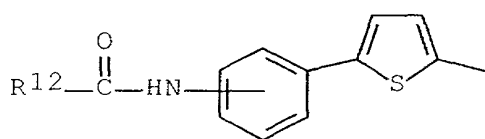
R^1 is halo (e.g. bromo, etc.), naphthyl (e.g. 2-naphthyl, etc.), phenyl (e.g. phenyl, etc.), mono- or dihalophenyl (e.g. 3(or 4)-chlorophenyl, 2(or 3 or 4)-fluorophenyl, 3,4-dichlorophenyl, 3,5-difluorophenyl, etc.), mono- or di(lower)alkylphenyl (e.g. 3(or 4)-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-(t-butyl)phenyl, 3,4-dimethylphenyl, etc.), lower alkoxyphenyl (e.g. 4-methoxyphenyl, 4-ethoxyphenyl, etc.), trihalo(lower)alkylphenyl (e.g. 4-trifluoromethylphenyl, etc.), trihalo(lower)alkoxyphenyl (e.g. 4-trifluoromethoxyphenyl, etc.), lower alkenylphenyl (e.g. 4-ethenylphenyl, etc.), lower alkylcarbamoylphenyl (e.g. 4-methylcarbamoylphenyl, 4-ethylcarbamoylphenyl, etc.), carbamoylphenyl (e.g. 4-carbamoylphenyl, etc.), phenyl(lower)alkylcarbamoylphenyl (e.g. 4-benzylcarbamoylphenyl, etc.), lower alkanoylphenyl (e.g. 4-acetylphenyl, etc.), lower alkylthiophenyl, lower alkylsulfinylphenyl, lower alkylsulfonylphenyl (e.g. 4-methylthiophenyl, 4-ethylthiophenyl, 4-methylsulfinylphenyl, 4-methylsulfonylphenyl, etc.),

phenylphenyl (e.g. phenylphenyl, etc.),
(halo)(phenyl)phenyl (e.g. 4-phenyl-3-fluorophenyl
etc.), halophenylphenyl (e.g. 4-(4-
fluorophenyl)phenyl etc.) hydroxyphenyl (e.g. 3(or
5 4)-hydroxyphenyl, etc.), mono- or
dihydroxy(lower)alkylphenyl,
phenoxy carbonyloxy(lower)alkylphenyl, (e.g. 3(or 4)-
hydroxymethylphenyl, 4-(1,2-dihydroxyethyl)phenyl,
4-(phenoxy carbonyloxymethyl)phenyl, etc.),
10 aminophenyl (e.g. 3(or 4)-aminophenyl, etc.),
carboxyphenyl (e.g. 4-carboxyphenyl, etc.), lower
alkylendioxyphenyl (e.g. 3,4-methylenedioxyphenyl,
etc.), lower alkanesulfonylamino phenyl (e.g.
4-(methanesulfonylamino)phenyl etc.), lower
15 alkenoylamino phenyl, (e.g. 3-(2-butenoylamino)phenyl,
etc.), lower cycloalkanecarbonylamino phenyl (e.g.
3-(cyclopropanecarbonylamino)phenyl,
3-(cyclobutanecarbonylamino)phenyl,
3-(cyclopentanecarbonylamino)phenyl, etc.)
20 phenyl(lower)alkoxyphenyl (e.g. 4-benzyloxyphenyl,
etc.), carbamoyl(lower)alkenylphenyl, mono- or
di(lower alkyl)carbamoyl(lower)alkenylphenyl (e.g.
4-(2-(methylcarbamoyl)ethenyl)phenyl,
4-(2-(ethylcarbamoyl)ethenyl)phenyl,
25 4-(2-(propylcarbamoyl)ethenyl)phenyl,
4-(2-(isopropylcarbamoyl)ethenyl)phenyl,
4-2-(dimethylcarbamoyl)ethenyl)phenyl, etc.)
phenylcarbamoyl(lower)alkenyl (e.g.
4-(2-(phenylcarbamoyl)ethenyl)phenyl, etc.),
30 lower alkoxycarbamoyl(lower)alkenyl (e.g.
4-(2-(methoxyphenylcarbamoyl)ethenyl)phenyl, etc.),
halophenylcarbamoyl(lower)alkenyl (e.g.
4-(2-(4-fluorophenylcarbamoyl)ethenyl)phenyl, etc.)
lower alkylcarbamoyloxyphenyl (e.g.
35 4-(methylaminocarbonyloxy)phenyl,

4-(ethylaminocarbonyloxy)phenyl, etc.),
lower alkanoyloxyphenyl (e.g. 4-propanoyloxyphenyl,
etc.) lower alkoxy(lower)alkanoyloxyphenyl (e.g.
4-(methoxyacetyloxy)phenyl, etc.)
5 lower alkoxy carbonyloxyphenyl (e.g.
4-(ethoxycarbonyloxy)phenyl, etc.)
pyridyl(lower)alkenoyloxyphenyl (e.g.
4-(3-(3-pyridyl)acryloyloxy)phenyl, etc.),
cyclo(lower)alkylcarbonyloxyphenyl (e.g.
10 4-(cyclopropylcarbonyloxy)phenyl, etc.),
carboxy(lower)alkoxyphenyl (e.g.
4-(carboxymethoxy)phenyl, etc.)
lower alkoxy carbonyl(lower)alkoxyphenyl (e.g.
4-(ethoxycarbonylmethoxy)phenyl,
15 4-(t-butoxycarbonylmethoxy)phenyl, etc.),
lower alkanoyl(lower)alkoxyphenyl (e.g.
4-(propanoylmethoxy)phenyl, etc.), lower
cycloalkanecarbamoyl(lower)alkoxyphenyl (e.g.
4-(cyclopropylcarbamoylmethoxy)phenyl, etc.),
20 lower alkylcarbamoyl(lower)alkoxyphenyl (e.g.
4-(methylcarbamoylmethoxy)phenyl,
4-(ethylcarbamoylmethoxy)phenyl,
4-(propylcarbamoylmethoxy)phenyl, etc.),
lower alkylcarbamoyloxy(lower)alkylphenyl (e.g.
25 3(or 4)-(methylcarbamoyloxymethyl)phenyl, etc.),
lower alkoxy carbonylamino(lower)alkylphenyl (e.g.
4-(methoxycarbonylaminomethyl)phenyl,
4-(t-butoxycarbonylaminomethyl)phenyl, etc.),
amino(lower)alkylphenyl (e.g. 4-aminomethylphenyl,
30 etc.), lower alkylcarbamoyl(lower)alkylphenyl (e.g.
4-(methylcarbamoylmethyl)phenyl, etc.),
furylcarbonylamino phenyl, 1,2,3,4-teretahydro-
isoquinolylcarbonylamino phenyl, N-Boc-1,2,3,4-
teretahydroisoquinolylcarbonylamino phenyl,
35 pyrrolidinylcarbonylamino phenyl (e.g.

3-(2(or 3)-furylcarbonylamino)phenyl,
 3-(1,2,3,4-teretahydroisoquinolylcarbonylamino)-
 phenyl, 3-(N-(t-butoxycarbonyl)-1,2,3,4-
 teretahydroisoquinolylcarbonylamino)phenyl,
 3-(pyrrolidinylcarbonylamino)phenyl, etc.),
 oxazolylphenyl (e.g. 4-(1,3-oxazolyl)phenyl, etc.),
 lower alkyloxadiazolylphenyl, (e.g. 4-(5-methyl-
 1,2,4-oxadiazol-3-yl)phenyl, etc.),

(b)



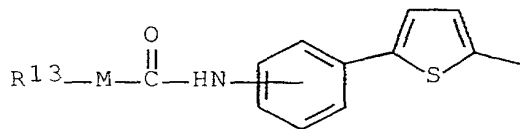
wherein

R¹² is lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, neopentyl, etc.) optionally substituted by the group consisting of phenyl (e.g. phenyl, etc.), halophenyl (e.g. 4-chlorophenyl, etc.), lower alkoxyphenyl (e.g. 4-methoxyphenyl, etc.), lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, isopropoxy, etc.), phenoxy (e.g. phenoxy, etc.), lower alkoxyphenoxy (e.g. 3(or 4)-methoxyphenoxy, etc.), halophenoxy (e.g. 4-fluoro(or chloro)phenoxy, etc.), lower alkylphenoxy (e.g. 3(or 4)-methylphenoxy, etc.), carboxy (e.g. carboxy, etc.), lower alkoxy carbonyl (e.g. methoxycarbonyl, t-butoxycarbonyl, etc.), lower alkyl carbamoyl (e.g. methyl carbamoyl, etc.), halo (e.g. chloro, etc.), lower alkenyloxy (e.g. allyloxy etc.), lower alkoxy(lower)alkoxy (e.g. 2-ethoxyethoxy, etc.), phenyl(lower)alkoxy (e.g. benzyloxy, etc.), piperidinyloxy (e.g. 4-piperidinyloxy, etc.), N-t-butoxycarbonylpiperidinyloxy (e.g. N-t-

butoxycarbonyl-4-piperidinyloxy, etc.), pyridyloxy (e.g. 3(or 4)-pyridyloxy, etc.), hydroxy (e.g. hydroxy, etc.), lower alkanoyloxy (e.g. acetoxy etc.), mono- or di(lower)alkylcarbamoyloxy (e.g. methylcarbamoyloxy, N-methyl-N-ethylcarbamoyloxy, etc.), piperidinylcarbonyloxy (e.g. piperidinocarbonyloxy, etc.), phenyl(lower)alkylcarbamoyloxy (e.g. benzylcarbamoyloxy, etc.), lower alkoxy-carbonylamino (e.g. methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, t-butoxycarbonylamino, etc.), amino (e.g. amino, etc.), lower alkoxy-carbonylamino (e.g. methoxycarbonylamino, t-butoxycarbonylamino, etc.), fluorenylmethoxycarbonylamino (e.g. fluorenylmethoxycarbonylamino etc.), mono- or di(lower)alkylamino (e.g. methylamino ethylamino dimethylamino, N-methyl-N-ethylamino t-butylamino, pentylamino etc.), N-lower alkyl-N-(lower alkoxy-carbonyl)amino (e.g. N-methyl-N-methoxycarbonylamino, N-methyl-N-t-butoxycarbonylamino N-ethyl-N-t-butoxycarbonylamino, etc.), N-lower alkyl-N-(fluorenylmethoxycarbonyl)amino (e.g. N-methyl-N-(fluorenylmethoxycarbonyl)amino etc.), N-lower alkyl-N-(mono- or di(lower)alkylcarbamoyl)amino (e.g. N-methyl-N-(dimethylcarbamoyl)amino, etc.), N-(mono- or di(lower alkyl)carbamoyl)amino (e.g. dimethylcarbamoylamino N-(ethylcarbamoyl)amino, etc.), benzoylamino (e.g. benzoylamino, etc.), lower alkanoylamino (e.g. acetylamino, isobutyrylamino, pivaloylamino, etc.), lower alkanesulfonylamino (e.g. methanesulfonylamino, etc.), lower alkoxy(lower)alkanoylamino (e.g. methoxyacetylamino, etc.),

cyclo(lower)alkyloxycarbonylamino (e.g. cyclopentyloxycarbonylamino, etc.), pyridylcarbonylamino (e.g. pyridylcarbonylamino, etc.), morpholinocarbonylamino (e.g. morpholinocarbonylamino, etc.), phenyl(lower)alkoxy carbonylamino (e.g. benzyloxycarbonylamino, etc.), lower alkoxyphenylsulfonylamino (e.g. 4-methoxyphenylsulfonylamino, etc.), hydroxy(lower)alkylamino (e.g. 2-hydroxyethylamino, etc.), morpholino (e.g. morpholino, etc.), oxooxazolidinyl (e.g. 2-oxo-1,3-oxazolidin-1-yl, etc.), oxopyrrolidinyl (e.g. 2-oxopyrrolidin-1-yl, etc.), trimethylhydantoinyl (e.g. 3,4,4-trimethylhydantoin-1-yl, etc.), pyridyl (e.g. 3(or 4)-pyridyl, etc.), lower alkenylamino (e.g. allylamino, etc.), lower alkoxy(lower)alkylamino (e.g. 2-ethoxyethylamino, etc.), phenyl(lower)alkylamino (e.g. benzylamino, etc.), pyridyl(lower)alkylamino (e.g. 3-pyridylmethylamino, etc.), and cyclo(lower)alkyl cyclohexyl, etc.),

(c)



30

wherein

M is oxygen or sulfur,

R^{13} is lower alkyl (e.g. methyl, ethyl, propyl,

isopropyl, etc.), phenyl(lower)alkyl (e.g.

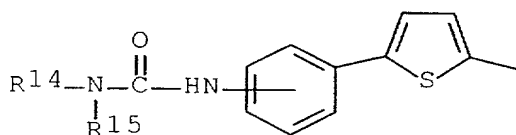
benzyl, etc.), lower alkoxy(lower)alkyl (e.g.

35

2-methoxyethyl, etc.), halo(lower)alkyl (e.g.

2-chloroethyl, etc.), amino(lower)alkyl, phthalimido(lower)alkoxycarbonylamino (e.g. 2-aminoethyl, 2-phthalimidoethyl, etc.), lower alkenyl (e.g. allyl, etc.), phenyl (e.g. phenyl, etc.),

(d)



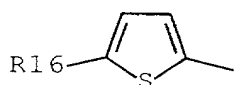
wherein

R¹⁵ is hydrogen, or lower alkyl (e.g. methyl, etc.),

R¹⁴ is hydrogen, lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, etc.), naphthyl (e.g. 1-naphthyl, etc.), halophenyl (e.g. 3(or 4)-chlorophenyl etc.), lower alkoxyphenyl (e.g. 4-methoxyphenyl, etc.), lower alkenyl (e.g. allyl, etc.),

cyclo(lower)alkyl(lower)alkyl (e.g. cyclohexylmethyl, etc.), phenyl(lower)alkyl (e.g. benzyl, etc.), halo(lower)alkyl (e.g. 2-chloroethyl, etc.), lower alkoxy(lower)alkyl (e.g. methoxymethyl, 2-methoxyethyl, etc.), hydroxy(lower)alkyl (e.g. 2-hydroxyethyl, etc.), (lower alkyl)(diphenyl)silyloxy(lower)alkyl (e.g. 2-((t-butyl)(diphenyl)silyloxy)ethyl, etc.), carboxy(lower)alkyl (e.g. carboxymethyl, etc.), lower alkoxycarbonyl(lower)alkyl (e.g. ethoxycarbonylmethyl, etc.), lower alkylcarbamoyl(lower)alkyl (e.g. methylcarbamoylmethyl, etc.), or pyridyl (e.g. 3-pyridyl, etc.),

(e)



5

wherein

R¹⁶ is benzothienyl (e.g. 2-benzothienyl, etc.), benzofuranyl (e.g. 2-benzofuranyl, etc.), thienyl (e.g. 2(or 3)-thienyl, etc.), furyl (e.g. 2-furyl, etc.), pyridyl (e.g. 3-pyridyl, etc.), lower alkylpyridyl (e.g. 1-methyl-4-pyridyl, 6-methyl-3-pyridyl, etc.), lower alkoxy pyridyl (e.g. 6-methoxy-3-pyridyl, etc.), lower alkoxy carbonylaminopyridyl (e.g. 5-methoxycarbonylamino-3-pyridyl, etc.), lower alkanoylthienyl (e.g. 5-acetyl-2-thienyl, etc.), lower alkyl carbamoylbenzofuranyl (e.g. 2-methylcarbamoyl-5-benzofuranyl, etc.).

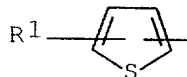
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(vi) The compounds (I) of the above (v), wherein

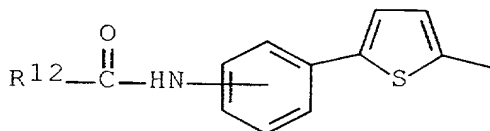
20

a group of the formula:



is the same group as (a), (c), (d) and (e) of claim 7, and the following formula (b):

25 (b)



30

wherein

R¹² is lower alkyl, phenyl(lower)alkyl, halophenyl(lower)alkyl, lower alkoxyphenyl(lower)alkyl, lower alkoxy(lower)alkyl, phenoxy(lower)alkyl, lower alkoxyphenoxy(lower)alkyl, halophenoxy(lower)alkyl,

35

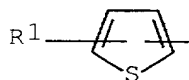
lower alkylphenoxy(lower)alkyl, carboxy(lower)alkyl,
lower alkoxycarbonyl(lower)alkyl, lower
alkylcarbamoyl(lower)alkyl, halo(lower)alkyl, lower
alkenyloxy(lower)alkyl, lower
5 alkoxy(lower)alkoxy(lower)alkyl,
phenyl(lower)alkoxy(lower)alkyl,
piperidinyloxy(lower)alkyl,
N-t-butoxycarbonylpiperidinyloxy(lower)alkyl,
pyridyloxy(lower)alkyl, hydroxy(lower)alkyl, lower
10 alkanoyloxy(lower)alkyl, mono- or
di(lower)alkylcarbamoyloxy(lower)alkyl,
piperidinylcarbonyloxy(lower)alkyl,
phenyl(lower)alkylcarbamoyloxy(lower)alkyl, lower
alkoxycarbonylamino(lower)alkyl, amino(lower)alkyl,
15 lower alkoxycarbonylamino(lower)alkyl,
fluorenylmethoxycarbonylamino(lower)alkyl, mono- or
di(lower)alkylamino(lower)alkyl, N-lower alkyl-N-
(lower alkoxycarbonyl)amino(lower)alkyl, N-lower
alkyl-N-(fluorenylmethoxycarbonyl)amino(lower)-
20 alkyl, N-lower alkyl-N-(mono- or di(lower)-
alkylcarbamoyl)amino(lower)alkyl, N-(mono- or
di(lower alkyl)carbamoyl)amino(lower)alkyl,
benzoylamino(lower)alkyl, lower
alkanoylamino(lower)alkyl, lower
25 alkanesulfonylamino(lower)alkyl, lower
alkoxy(lower)alkanoylamino(lower)alkyl,
cyclo(lower)alkyloxycarbonylamino(lower)alkyl,
pyridylcarbonylamino(lower)alkyl,
morpholinocarbonylamino(lower)alkyl,
30 phenyl(lower)alkoxycarbonylamino(lower)alkyl, lower
alkoxyphenylsulfonylamino(lower)alkyl,
hydroxy(lower)alkylamino(lower)alkyl,
morpholino(lower)alkyl, oxooxazolidinyl(lower)alkyl,
oxopyrrolidinyl(lower)alkyl,
35 trimethylhydantoinyl(lower)alkyl,

pyridyl(lower)alkyl, lower alkenylamino(lower)alkyl,
lower alkoxy(lower)alkylamino(lower)alkyl,
phenyl(lower)alkylamino(lower)alkyl,
pyridyl(lower)alkylamino(lower)alkyl,
5 cycl(lower)alkyl, (amino)(phenyl)(lower)alkyl (e.g.
2-phenyl-1-aminoethyl, etc.), (lower
alkoxycarbonylamino)(phenyl)(lower)alkyl (e.g. 1-
amino-1-phenylmethyl, 1-t-butoxycarbonylamino-1-
phenylmethyl, 1-amino-2-phenylethyl, 1-t-
10 butoxycarbonylamino-2-phenylethyl, etc.),
(amino)(lower alkoxy)(lower)alkyl (e.g. 1-amino-2-
methoxyethyl, etc.), (lower alkoxycarbonylamino)-
(lower alkoxy)(lower)alkyl (e.g. 1-t-
butoxycarbonylamino-2-methoxyethyl, etc.),
15 (amino)(carboxy)(lower)alkyl, (lower
alkoxycarbonylamino)(carboxy)(lower)alkyl,
(amino)(lower alkoxycarbonyl)(lower)alkyl, (lower
alkoxycarbonylamino)(lower alkoxycarbonyl)-
(lower)alkyl (e.g. 1-amino-3-carboxypropyl, 1-t-
20 butoxycarbonylamino-3-carboxypropyl, 1-amino-3-(t-
butoxycarbonyl)propyl, 1-t-butoxycarbonylamino-3-t-
butoxycarbonylpropyl, etc.)
(amino)(phenyl(lower)alkoxy)(lower)alkyl, (lower
alkoxycarbonylamino)(phenyl(lower)alkoxy)-
25 (lower)alkyl (e.g. 1-amino-2-benzyloxyethyl, 1-t-
butoxycarbonylamino-2-benzyloxyaminoethyl, etc.),
(amino)(pyridyl)(lower)alkyl, (lower
alkoxycarbonylamino)(pyridyl)(lower)alkyl (e.g. 1-
amino-2-(3-pyridyl)ethyl, 1-t-butoxycarbonylamino-
30 2-(3-pyridyl)ethyl, 1-amino-2-(4-pyridyl)ethyl, 1-
t-butoxycarbonylamino-2-(4-pyridyl)ethyl, etc.),
(amino)(hydroxy)(lower)alkyl, (lower
alkoxycarbonylamino)(hydroxy)(lower)alkyl (e.g. 1-
amino-2-hydroxyethyl, 1-t-butoxycarbonylamino-2-
35 hydroxyethyl, etc.), (amino)(amino)(lower)alkyl,

(lower alkoxycarbonylamino) (amino) (lower) alkyl,
(amino) (lower alkoxycarbonylamino) (lower) alkyl,
(lower alkoxycarbonylamino) (lower
alkoxy carbonylamino) (lower) alkyl (e.g. 1,5-
diaminopentyl, 1-t-butoxycarbonylamino-5-
aminopentyl, 1,5-bis(t-butoxycarbonylamino)pentyl,
1-amino-5-(t-butoxycarbonylamino)pentyl, etc.),
(amino) (lower cycloalkane) (lower) alkyl, (lower
alkoxy carbonylamino) (lower cycloalkane) (lower) alkyl
(e.g. 1-amino-2-cyclohexylethyl, 1-t-
butoxycarbonylamino-2-cyclohexylethyl, etc.).

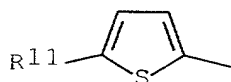
(vii) The compounds (I) of the above (vi), wherein

a group of the formula:



is the group of the following formula (a) to (e):

(a)



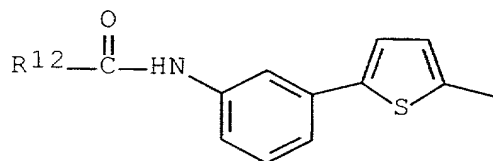
wherein

R¹¹ is bromo, 2-naphthyl, phenyl,
3(or 4)-chlorophenyl, 2(or 3 or 4)-fluorophenyl,
3,4-dichlorophenyl, 3,5-difluorophenyl,
3(or 4)-methylphenyl, 4-ethylphenyl,
4-isopropylphenyl, 4-(t-butyl)phenyl,
3,4-dimethylphenyl, 4-methoxyphenyl,
4-ethoxyphenyl, 4-trifluoromethylphenyl,
4-trifluoromethoxyphenyl, 4-ethenylphenyl,
4-methylcarbamoylephenyl, 4-ethylcarbamoylephenyl, 4-
carbamoylephenyl, 4-benzylcarbamoylephenyl,

- 4-acetylphenyl, 4-methylthiophenyl,
4-ethylthiophenyl, 4-methylsulfinylphenyl,
4-methylsulfonylphenyl, phenylphenyl, 4-phenyl-3-
5 hydroxyphenyl, 4-(4-fluorophenyl)phenyl, 3(or 4)-
hydroxyphenyl, 3(or 4)-hydroxymethylphenyl,
4-(1,2-dihydroxyethyl)phenyl,
4-(phenoxy carbonyloxymethyl)phenyl, 3(or 4)-
aminophenyl, 4-carboxyphenyl,
3,4-methylenedioxyphenyl,
10 4-(methanesulfonylamino)phenyl,
3-(2-butenoylamino)phenyl,
3-(cyclopropanecarbonylamino)phenyl,
3-(cyclobutanecarbonylamino)phenyl,
3-(cyclopentanecarbonylamino)phenyl,
15 4-benzyloxyphenyl,
4-(2-(methylcarbamoyl)ethenyl)phenyl,
4-(2-(ethylcarbamoyl)ethenyl)phenyl,
4-(2-(propylcarbamoyl)ethenyl)phenyl,
4-(2-(isopropylcarbamoyl)ethenyl)phenyl,
20 4-2-(dimethylcarbamoyl)ethenyl)phenyl,
4-(2-(phenylcarbamoyl)ethenyl)phenyl,
4-(2-(methoxyphenylcarbamoyl)ethenyl)phenyl,
4-(2-(4-fluorophenylcarbamoyl)ethenyl)phenyl,
4-(methylaminocarbonyloxy)phenyl,
25 4-(ethylaminocarbonyloxy)phenyl,
4-propanoyloxyphenyl, 4-(methoxyacetyloxy)phenyl,
4-(ethoxycarbonyloxy)phenyl,
4-(3-(3-pyridyl)acryloyloxy)phenyl,
4-(cyclopropylcarbonyloxy)phenyl,
30 4-(carboxymethoxy)phenyl,
4-(ethoxycarbonylmethoxy)phenyl,
4-(t-butoxycarbonylmethoxy)phenyl,
4-(propanoylmethoxy)phenyl,
4-(cyclopropylcarbamoylmethoxy)phenyl,
35 3(or 4)-(methylcarbamoylmethoxy)phenyl,

4-(ethylcarbamoylmethoxy)phenyl,
 4-(propylcarbamoylmethoxy)phenyl,
 3(or 4)-(methylcarbamoyloxymethyl)phenyl,
 4-(methoxycarbonylaminomethyl)phenyl,
 4-(t-butoxycarbonylaminomethyl)phenyl,
 4-aminomethylphenyl,
 4-(methylcarbamoylmethyl)phenyl,
 3-(2(or 3)-furylcarbonylamino)phenyl, 3-(1,2,3,4-
 teretahydroisoquinolylcarbonylamino)phenyl,
 3-(N-(t-butoxycarbonyl)-1,2,3,4-
 teretahydroisoquinolylcarbonylamino)phenyl,
 3-(pyrrolidinylcarbonylamino)phenyl,
 4-(1,3-oxazolyl)phenyl,
 4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl,

(b)

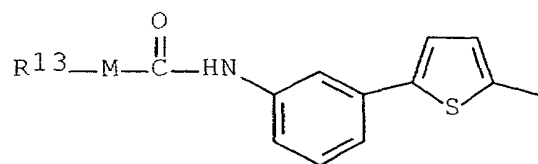


wherein

R¹² is methyl, ethyl, propyl, isopropyl, butyl,
 isobutyl, t-butyl, neopentyl, phenylmethyl,
 4-chlorophenylmethyl, 4-methoxyphenylmethyl,
 methoxymethyl, ethoxymethyl, propoxymethyl,
 butoxymethyl, isopropylloxymethyl, 1-methoxyethyl,
 2-methoxyethyl, phenoxymethyl, 2-phenoxyethyl, 3(or
 4)-methoxyphenoxymethyl, 4-fluoro(or
 chloro)phenoxymethyl, 3(or 4)-methylphenoxymethyl,
 2-carboxyethyl, 2-methoxycarbonylethyl, 2-t-
 butoxycarbonylethyl, 2-methylcarbamoylethyl,
 2-chloroethyl, chloromethyl, allyloxymethyl,
 (2-ethoxyethoxy)methyl, benzyloxymethyl,
 4-piperidinyloxymethyl, (N-t-butoxycarbonyl-4-

5 piperidinyl)oxymethyl, 3(or 4)-pyridyloxymethyl,
hydroxymethyl, 2-hydroxyethyl, acetoxymethyl,
1-acetoxyethyl, methylcarbamoyloxymethyl, 1-(N-
methyl-N-ethylcarbamoyloxy)methyl, (piperidino-
carbonyloxy)methyl, (benzylcarbamoyloxy)methyl,
(t-butoxycarbonylamino)methyl, aminomethyl,
1-aminoethyl, 1-(t-butoxycarbonylamino)ethyl,
2-aminoethyl, methoxycarbonylaminomethyl,
2-(methoxycarbonylamino)ethyl,
10 ethoxycarbonylaminomethyl,
propoxycarbonylaminomethyl,
1-(fluorenylmethoxycarbonylamino)methyl,
2-(t-butoxycarbonylamino)ethyl,
2-(fluorenylmethoxycarbonylamino)ethyl,
15 1-aminoisopropyl, 1-aminopropyl,
1-(t-butoxycarbonylamino)propyl,
1-(t-butoxycarbonylamino)isopropyl,
1,5-diaminopentyl, 1,5-bis(t-butoxycarbonylamino)-
pentyl, methylaminomethyl, ethylaminomethyl,
20 3-(2-(N-methyl-N-ethylamino)methyl,
3-(dimethylaminomethyl, 3-(pentylaminomethyl,
3-(t-butylaminomethyl, 3-(3-methylaminoethyl,
3-(2-(N-methyl-N-methoxycarbonylamino)methyl,
1-(N-methyl-N-t-butoxycarbonylamino)methyl,
25 1-(N-ethyl-N-t-butoxycarbonylamino)methyl,
2-(N-methyl-N-(fluorenylmethoxycarbonyl)amino)-
ethyl, 2-(N-methyl-N-(t-butoxycarbonyl)amino)ethyl,
1-(N-methyl-N-(dimethylcarbamoyl)amino)methyl,
1-(dimethylcarbamoylamino)methyl,
30 1-(N-(ethylcarbamoyl)amino)methyl,
2-(N-(ethylcarbamoyl)amino)ethyl,
benzoylaminomethyl, 2-benzoylaminoethyl,
acetylaminomethyl, isobutyrylaminomethyl,
pivaloylaminomethyl,
35 1-(methanesulfonylamino)methyl,

2-(methanesulfonylamino)ethyl,
methoxyacetylaminomethyl,
cyclopentylloxycarbonylaminomethyl,
pyridylcarbonylaminomethyl,
5 morpholinocarbonylaminomethyl,
benzyloxycarbonylaminomethyl,
1-(4-methoxyphenylsulfonylamino)methyl,
1-(2-hydroxyethylamino)methyl,
morpholinomethyl, 1-(2-oxo-1,3-oxazolidin-1-
10 yl)methyl, 1-(2-oxopyrrolidin-1-yl)methyl,
1-(3,4,4-trimethylhydantoin-1-yl)methyl,
allylaminomethyl, 1-(2-ethoxyethylamino)methyl,
benzylaminomethyl, 1-(3-pyridylmethylamino)methyl,
2-phenyl-1-aminoethyl, 1-amino-1-phenylmethyl,
15 1-t-butoxycarbonylamino-1-phenylmethyl,
1-amino-2-phenylethyl, 1-t-butoxycarbonylamino-2-
phenylethyl, 1-amino-2-methoxyethyl,
1-t-butoxycarbonylamino-2-methoxyethyl, 1-amino-3-
carboxypropyl, 1-t-butoxycarbonylamino-3-
20 carboxypropyl, 1-amino-3-(t-butoxycarbonyl)propyl,
1-t-butoxycarbonylamino-3-t-butoxycarbonylpropyl,
etc.), 1-amino-2-benzyloxyethyl,
1-t-butoxycarbonylamino-2-benzyloxyaminoethyl,
1-amino-2-(3-pyridyl)ethyl, 1-t-
25 butoxycarbonylamino-2-(3-pyridyl)ethyl, 1-amino-2-
(4-pyridyl)ethyl, 1-t-butoxycarbonylamino-2-(4-
pyridyl)ethyl, 1-amino-2-hydroxyethyl,
1-t-butoxycarbonylamino-2-hydroxyethyl,
(1,5-diaminopentyl, 1-t-butoxycarbonylamino-5-
30 aminopentyl, 1,5-bis(t-butoxycarbonylamino)pentyl,
1-amino-5-(t-butoxycarbonylamino)pentyl, 1-amino-2-
cyclohexylethyl, 1-t-butoxycarbonylamino-2-
cyclohexylethyl,



5

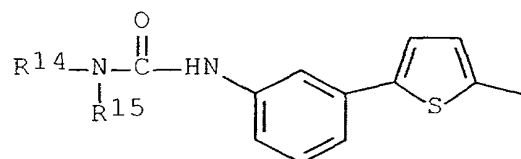
wherein

M=O and R¹³ is methyl, ethyl, propyl, isopropyl, benzyl, 2-methoxyethyl, 2-chloroethyl, 2-aminoethyl, 2-phthalimidoethyl, allyl, phenyl, or

M=S and R¹³ is methyl, ethyl,

10

(d)



15

wherein

R¹⁵ is hydrogen and

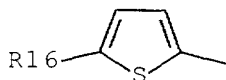
R¹⁴ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, 1-naphthyl, 3(or 4)-chlorophenyl, 3-methoxyphenyl, allyl, cyclohexylmethyl, benzyl, 2-chloroethyl, methoxymethyl, 2-methoxyethyl, 2-hydroxyethyl, 2-((t-butyl)(diphenyl)silyloxy)ethyl, carboxymethyl, ethoxycarbonylmethyl, methylcarbamoylmethyl, or 3-pyridyl,

20

R¹⁴ is ethyl and R¹⁵ is methyl,

25

(e)



30

35

wherein

R¹⁶ is 2-benzothienyl, 2-benzofuranyl, 2(or 3)-thienyl,

2-furyl, 3-pyridyl, 1-methyl-4-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 5-methoxycarbonylamino-3-pyridyl, 5-acetyl-2-thienyl, 2-methylcarbamoyl-5-benzofuranyl.

5

The processes for preparing the object compounds are explained in detail in the following.

Process 1

10 The object compound (I-b) or a salt thereof can be prepared by subjecting a compound (I-a) or a salt thereof to removal reaction of the carboxy-protective group.

Suitable salts of the compounds (I-a) and (I-b) can be referred to the ones as exemplified for the compound (I).

15 This reaction is carried out in accordance with a conventional method such as solvolysis including hydrolysis, reduction or the like.

The solvolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

20 Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, lithium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

25 Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, boron trifluoride diethyl etherate, hydrogen iodide, etc.].

30 The removal reaction using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid,

trifluoroacetic acid, etc.] or the like, is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, carbon tetrachloride, dioxane, tetrahydrofuran, N,N-dimethylformamide, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the removal reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction may include a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like, and these catalysts may be used in a combination with ammonium formate (e.g. a

combination of palladium on carbon and ammonium formate, etc.).

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process 2

The compound (I-b) or a salt thereof can be prepared by oxidating the compound (II) or a salt thereof.

Suitable salts of the compound (II) may be the same as those for the compound (I).

Oxidation is carried out in a conventional manner, which is capable of oxidating a vinyl group to a carboxy group, and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, potassium periodate, etc.), peroxy acid such as perbenzoic acid (e.g., perbenzoic acid, m-chloroperbenzoic acid, etc.), OXONE ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$), potassium permanganate, a combination of titanium (III) chloride and hydrogen peroxide, a combination thereof (e.g. a combination of potassium permanganate and sodium periodate, etc.), and the like.

This reaction can be carried out in the presence of a suitable base as mentioned above (e.g. potassium carbonate, etc.).

The reaction is usually carried out in a conventional

solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other
5 organic solvent which does not adversely affect the reaction.

Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

10

Process 3

The compound (I-d) or a salt thereof can be prepared by subjecting the compound (I-c) or a salt thereof to a reduction reaction.

15

Suitable salts of the compounds (I-c) and (I-d) may be the same as those for the compound (I).

The reduction method applicable for this reaction may be the same as Process 1, which is capable of converting haloaryl group to aryl group (e.g. a combination of
20 palladium on carbon and ammonium formate, etc.).

Process 4

The compound (I-e) or a salt thereof can be prepared by reacting the compound (I-b) or its reactive derivative at
25 the carboxy group, or a salt thereof with compound (IV) or its reactive derivative at the amino group, or a salt thereof.

Suitable reactive derivative at the amino group of the compound (IV) may include Schiff's base type imino or its
30 tautomeric enamine type isomer formed by the reaction of the compound (IV) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IV) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide,
35 bis(trimethylsilyl)urea or the like; a derivative formed by

reaction of the compound (IV) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (IV) and its reactive
5 derivative can be referred to the acid addition salts as exemplified for the compound (I).

Suitable salts of the compound (I-e) may be the same as those for the compound (I).

Suitable reactive derivative at the carboxy group of
10 the compound (I-b) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride which acid such as substituted phosphoric acid [e.g.
15 dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic
20 acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with
25 imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N^+=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester,
30 trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy
35 compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-

pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (I-b) to be used.

5 The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent
10 which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

 In this reaction, when the compound (I-b) is used in a free acid form or its salt form, the reaction is preferably
15 carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide;
20 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCD); N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite;
25 ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-
30 hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-isoxazolium hydroxide intramolecular salt; N-hydroxybenzotriazole; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with
35 thionyl chloride, phosgene, trichloromethyl chloroformate,

phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base as mentioned above such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine,
5 N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, alkali metal hydroxide, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

10 Process 5

The object compound (I-f) or a salt thereof can be prepared by cyclizing the compound (III) or a salt thereof.

Suitable salts of the compounds (I-f) and (III) may be the same as those for the compound (I).

15 This reaction is preferably carried out in the presence of hydrogen halide (e.g. hydrogen iodide, etc.) or alkali metal halide (e.g. sodium iodide, etc.).

This reaction can be carried out in the presence of a suitable base as mentioned above such as alkali metal
20 hydroxide.

The reaction can be carried out in a conventional solvent, which does not adversely influence the reaction as mentioned above such as water, tetrahydrofuran, alcohol (e.g. methanol, ethanol, etc.), a mixture thereof, and the like.

25 The reaction temperature is not critical and the reaction can be carried out under from warming to heating.

Process 6

The compound (I-g) or a salt thereof can be prepared by
30 reacting the compound (I-b) or its reactive derivative at the carboxy group, or a salt thereof, with an optically active amine or its reactive derivative at the amino group, or a salt thereof.

Suitable "optically active amine" may include a
35 conventional one which is capable of separating the starting

racemic compound into each optically active compound such as (R)-(+)- α -methylbenzylamine, and the like.

Suitable salts of the compound (I-g) may be the same as those exemplified for the compound (I).

- 5 Suitable salts of the optically active amine may be acid addition salts as mentioned for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride,
10 tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and dichloromethane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

This reaction can be carried out in the presence of an
15 organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g., calcium, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkaline earth metal hydride (e.g., calcium hydride, etc.), alkali metal hydroxide (e.g., sodium hydroxide,
20 potassium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal
25 alkanoic acid (e.g., sodium acetate, etc.), trialkylamine (e.g., triethylamine, etc.), pyridine compound (e.g., pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, lithium diisopropylamide, and the like.

Suitable reactive derivative at the amino group of
30 optically active amine may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the said amine with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the said amine with a silyl compound such as
35 bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide,

bis(trimethylsilyl)urea or the like; a derivative formed by the reaction of the said amine with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group and
5 salts of the compound (I-b) may be the same as mentioned above.

The reaction is preferably carried out in the presence of a conventional condensing agent such as

- N,N'-dicyclohexylcarbodiimide;
10 N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide;
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;
N,N'-carbonylbis-(2-methylimidazole);
15 pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine; ethoxyacetylene;
1-alkoxy-1-chloroethylene; trialkyl phosphite;
ethyl polyphosphate; isopropyl polyphosphate;
phosphorus oxychloride (phosphoryl chloride);
20 phosphorus trichloride; diphenyl phosphorylazide;
thionyl chloride; oxalyl chloride; lower alkyl haloformate
(e.g., ethyl chloroformate, isopropyl chloroformate);
triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt;
2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide
25 intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-
chloro-1H-benzotriazole; 1-hydroxybenzotriazole; or so-
called Vilsmeier reagent prepared by the reaction of N,N-
dimethylformamide with thionyl chloride, phosgene,
trichloromethyl chloroformate, phosphorus oxychloride or
30 oxalyl chloride.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 7

- 35 The compound (I-i) or a salt thereof can be prepared by

subjecting the compound (I-h) or a salt thereof to a removal reaction of the hydroxy protective group.

Suitable salts of the compounds (I-h) and (I-i) may be the same as those exemplified for the compound (I).

- 5 The reaction of this process can be carried out in a manner similar to that in Process 1.

Process 8

- 10 The compound (I-k) and a salt thereof can be prepared by oxidating the compound (I-j) or a salt thereof.

Suitable salts of the compounds (I-j) and (I-k) may be the same as those exemplified above with regard to the compound (I).

- 15 Suitable method of this oxidation includes conventional ones, which can convert thia group to sulfinyl or sulfonyl group, or sulfinyl to sulfonyl group, such as exemplified for Process 2.

Process 9

- 20 The compound (I-l) or a salt thereof can be prepared by reacting the compound (I-c) or a salt thereof with the compound (V).

Suitable salts of the compound (I-l) may be the same as those exemplified for the compound (I).

- 25 The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and dichloromethane, a mixture thereof, or any
30 other organic solvents which do not adversely affect the reaction.

- This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g., lithium, sodium, potassium, etc.), alkaline earth metal
35 (e.g., calcium, etc.), alkali metal hydride (e.g., sodium

hydride, etc.), alkaline earth metal hydride (e.g., calcium hydride, etc.), alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g., sodium acetate, etc.), trialkylamine (e.g., triethylamine, etc.), pyridine compound (e.g., pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, lithium diisopropylamide, alkali metal halide (e.g., sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g., sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g., diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.), and the like.

The reaction is preferably carried out in the presence of a conventional condensing agent such as

N,N'-dicyclohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide;
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;

N,N'-carbonylbis-(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine; ethoxyacetylene;
1-alkoxy-1-chloroethylene; trialkyl phosphite;
ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride);
phosphorus trichloride; diphenyl phosphorylazide;
thionyl chloride; oxalyl chloride; lower alkyl haloformate (e.g., ethyl chloroformate, isopropyl chloroformate);
triphenylphosphine; etrakis(triphenylphosphine)palladium(0);
2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-

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Process 12

The compound (I-o) or a salt thereof can be prepared by reacting the compound (IX) or a salt thereof with the compound (X).

Suitable salts of the compounds (I-o) and (IX) may be the same as those exemplified for the compound (I).

This reaction can be carried out in the presence of a suitable acid as exemplified for Process 1, wherein preferable one may be boron trifluoride diethyl etherate, and the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and dichloromethane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

20 Process 13

The compound (I-q) or a salt thereof can be prepared by amidating the compound (I-p) or its reactive derivative at the carboxy group, or a salt thereof.

Suitable salts of the compounds (I-p) and (I-q) may be the same as those for the compound (I).

Suitable reactive derivative of the compound (I-p) may be the same as those for the compound (I-b).

The amidation reaction applicable to this process may include a conventional amidation reaction which can convert a carboxy-group to an amido-group, for example, reaction with an optionally substituted amines such as mono- or di(lower)alkylamine (e.g. methylamine, etc.), and the like.

And the reaction can be carried out in substantially the same manner as described in Process 4.

Process 14

The compound (I-s) or a salt thereof can be prepared by acylating the compound (I-r) or its reactive derivative at the amino group, or a salt thereof.

- 5 Suitable salts of the compounds (I-r) and (I-s) may be the same as those for the compound (I).

- 10 Suitable acylating agent used in this reaction may be a conventional acylating agent which is capable of introducing the acyl group as mentioned before such as carboxylic acid, carbonic acid, sulfonic acid and their reactive derivative, for example, an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Preferable example of such reactive derivative may include acid chloride, acid
- 15 bromide, a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid,
- 20 sulfuric acid, alkyl carbonate (e.g. methyl carbonate, ethyl carbonate, propyl carbonate, etc.), aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.), aromatic carboxylic acid (e.g. benzoic acid, etc.), a symmetrical
- 25 acid anhydride, an activated acid amide with a heterocyclic compound containing imino function such as imidazole, 4-substituted imidazole, dimethylpyrazole, triazole and tetrazole, an activated ester (e.g. p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester,
- 30 pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyridyl ester, piperidiny ester, 8-quinolyl thioester, or an ester with a N-hydroxy compound such as N,N-dimethylhydroxylamine,
- 35 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide,

N-hydroxyphthalimide, 1-hydroxybenzotriazole, 1-hydroxy-6-chlorobenzotriazole, etc.), isocyanic acid or a salt thereof (e.g. sodium isocyanate, etc.), lower alkylisocyanate (e.g. methylisocyanate, ethylisocyanate, etc.), and the like.

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This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g. lithium, sodium potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.),
10 alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate,
15 etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.),
20 quinoline, and the like.

In case that the acylating agent is used in a free form or its salt in this reaction, the reaction is preferably carried out in the presence of a condensing agent such as a
25 carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.], a ketenimine compound (e.g. N,N'-carbonylbis(2-
30 methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, etc.); an olefinic or acetylenic ether compounds (e.g. ethoxyacetylene, β -chlorovinylethyl ether), a sulfonic acid ester of N-hydroxybenzotriazole derivative [e.g. 1-(4-
35 chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, etc.],

a combination of trialkylphosphite or triphenylphosphine and carbon tetrachloride, disulfide or diazenedicarboxylate (e.g. diethyl diazenedicarboxylate, etc.), a phosphorus compound (e.g. ethyl polyphosphate, isopropyl polyphosphate, phosphoryl chloride, phosphorus trichloride, etc.), thionyl chloride, oxalyl chloride, N-ethylbenzisoaxazolium salt, N-ethyl-5-phenylisoxazolium-3-sulfonate, a reagent (referred to a so-called "Vilsmeier reagent") formed by the reaction of an amide compound such as N,N-di(lower)alkylformamide (e.g. dimethylformamide, etc.), N-methylformamide or the like with a halogen compound such as thionyl chloride, phosphoryl chloride, phosgene or the like, and the like.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

Process 15

The compound (I-r) or a salt thereof can be prepared by subjecting the compound (I-t) or a salt thereof to a removal reaction of the amino-protective group.

Suitable salts of the compound (I-t) may be the same as those for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 1.

Process 16

The compound (I-v) or a salt thereof can be prepared by subjecting the compound (I-u) or a salt thereof to a removal reaction of the hydroxy-protective group.

Suitable salts of the compounds (I-u) and (I-v) may be the same as those for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 1.

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Process 17

The compound (I-x) or a salt thereof can be prepared by oxidating the compound (I-w) or a salt thereof.

10 Suitable salts of the compounds (I-w) and (I-x) may be the same as those for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 8.

Process 18

15 The compound (I-z) or a salt thereof can be prepared by reducing the compound (I-y) or a salt thereof.

Suitable salts of the compounds (I-y) and (I-z) may be the same as those for the compound (I).

20 The reaction of this process can be carried out in a manner similar to that in Process 3.

Process 19

The compound (I-ab) or a salt thereof can be prepared by oxidating the compound (I-aa) or a salt thereof.

25 Suitable salts of the compounds (I-aa) and (I-ab) may be the same as those for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 2.

30 Process 20

The compound (I-ac) or a salt thereof can be prepared by acylating the compound (I-v) or a salt thereof.

Suitable salts of the compound (I-ac) may be the same as those for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 14.

Process 21

5 The compound (I-ad) or a salt thereof can be prepared by reacting the compound (XI) or a salt thereof with the compound (XII) or a salt thereof.

Suitable salts of the compounds (I-ad), (XI) and (XII) may be the same as those for the compound (I).

10 The reaction of this process can be carried out in a manner similar to that in Process 9.

Process 22

15 The compound (I-p) or a salt thereof can be prepared by subjecting the compound (I-ae) or a salt thereof to a removal reaction of the carboxy-protective group.

Suitable salts of the compound (I-ae) may be the same as those for the compound (I).

20 The reaction of this process can be carried out in a manner similar to that in Process 1.

Process 23

25 The compound (I-ag) or a salt thereof can be prepared by reacting the compound (I-af) or a salt thereof with a substituted amine.

Suitable salts of the compounds (I-af) and (I-ag) may be the same as those for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 4.

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The compounds obtained above can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation and the like.

35 The object compounds can be transformed into their

salts in a conventional manner.

It is to be noted that the object compounds may include one or more stereoisomers or optical isomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

Collagenases initiate the degradation of collagen in vertebrates and, in addition to their normal function in the metabolism of connective tissue and wound healing, they have been implicated to be involved in a number of pathological conditions such as joint destruction in rheumatoid arthritis, periodontal disease, corneal ulceration, tumor metastasis, osteoarthritis, decubitus restenosis after percutaneous transluminal coronary angioplasty, osteoporosis, psoriasis, chronic active hepatitis, autoimmune keratitis, and the like, and therefore the compounds of the present invention are useful for treating and/or preventing such pathological conditions.

Inhibitory activity of MMP can be assayed by a conventional test method as mentioned below.

Test Methods:

Test Method 1:

Inhibitory activity of human MMP-1

Human collagenase was prepared from the culture medium of human skin fibroblast stimulated with interleukin-1 β (1 ng/ml). Latent collagenase was activated by incubation with trypsin (200 μ g/ml) at 37°C for 60 minutes and the reaction was stopped by adding soybean trypsin inhibitor (800 μ g/ml). Collagenase activity was determined using FITC-labeled calf skin type I collagen. FITC-collagen (2.5 mg/ml) was incubated at 37°C for 120 minutes with the activated collagenase and test compound in 50 mM Tris buffer (containing 5 mM CaCl₂, 200 mM NaCl and 0.02% NaN₃, pH 7.5). After stopping the enzyme reaction by adding the equal

volume of 70% ethanol-200 mM Tris buffer (pH 9.5), the reaction mixture was centrifuged, and collagenase activity was estimated by measuring the fluorescence intensity of supernatant at 495 nm (excitation) and 520 nm (emission).

5

Test Method 2:

Inhibitory activity of human MMP-9

The inhibitory activity of test compounds against human MMP-9 were measured by using commercial kits (Yagai, Japan).

10 Gelatinolytic activity was determined by monitoring the degradation of FITC-labeled bovine type IV collagen after incubation for 4 hours at 42°C. The amount of degraded collagen was estimated by measuring the fluorescence intensity at 495 nm (excitation) and 520 nm (emission).

15

Test Method 3:

Inhibitory activity of human MMP-13

The inhibitory potential of test compounds against human MMP-13 were assayed by using commercial kit (Chondrex, USA) contained truncated form of human recombinant MMP-13 and fluorogenic peptide substrate. Activity of human MMP-13 was determined by monitoring the degradation of fluorogenic peptide substrate after incubation for 1 hour at 35°C and estimated by measuring the fluorescence intensity of degraded peptide substrate at 495 nm (excitation) and 520 nm (emission).

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Test Method 4:

Inhibitory activity of human MMP-8

30 The inhibitory potential of test compounds against human MMP-8 were assayed by using commercial kit (Chondrex, USA) contained recombinant human pro-MMP-8 and FITC-labeled telopeptide-free soluble bovine type I collagen as a substrate. Recombinant human pro-MMP-8 was activated by a sequential incubation with mercury compound and proteinase

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at 35°C for 1 hour. Reaction mixture containing the activated MMP-8, substrate and test compounds were incubated at 35°C for 2 hours. After stopping the enzyme reaction by adding the stop solution (o-phenathroline), the reaction mixture was centrifuged and MMP-8 activity was estimated by measuring the fluorescence intensity of supernatant at 490 nm (excitation) and 520 nm (emission).

For therapeutic purposes, the compounds and pharmaceutically acceptable salts thereof of the present invention can be used in the form of a pharmaceutical preparation containing, as an active ingredient, one of said compounds in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solutions, suspensions, emulsions, sublingual tablets, suppositories, ointments, and the like. If desired, there may be included, in these preparations, auxiliary substances, stabilizing agents, wetting agents, emulsifying agents, buffers and other commonly used additives.

While the dose of the compound will vary depending upon the age and condition of patient and the like, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the active ingredient per kg weight of a human being, and in the case of intramuscular administration, a daily dose of 0.05 - 100 mg of the same per kg weight of a human being, or in the case of oral administration, a daily dose of 0.1 - 100 mg of the same per kg weight of a human being, is generally given for the treatment of MMP or TNF α -mediated diseases.

In order to illustrate the usefulness of the object compound, the pharmacological test data of a representative compound of the compounds are shown in the following.

Inhibitory activity of MMP

1. Test Method

Inhibitory activity of human MMP-13 as mentioned above.

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2. Test Compound

Compound of Example 15

3. Test Result

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Test Compound	Inhibitory activity [IC ₅₀ (nM)]
Example 15	2.2

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

15

The abbreviations used in this description are, for example, as follows.

Aib: aminoisobutyric acid

Abu: aminobutyric acid

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4PyAla: 4-pyridylalanine

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Preparation 1-1)

N-Chlorosuccinimide (2.67 g) was added gradually over 30 minutes to a stirred solution of tetrahydro-2H-thiopyran (2.04 g) in benzene (20 ml). The temperature was maintained at 20-30°C by intermittent external cooling. The mixture was stirred for 1 hour and rapidly filtered to remove succinimide. The filtrate was added to a solution of 4-anisylmagnesium bromide in diethyl ether which was prepared from 4-anisyl bromide (7.48 g) and magnesium turnings (0.875 g) in diethyl ether (36 ml) in a usual manner. The rate of addition was such that the temperature of the reaction was maintained between 10-15°C. The resultant mixture was stirred at room temperature for 17 hours and decomposed by the addition of ice and a 20% aqueous solution of sulfuric acid. The organic layer was separated, washed twice with water, once with 1N sodium hydroxide solution, twice with water, then once with brine, and dried over magnesium sulfate. Removal of the solvent, followed by washing with methanol, gave 3,4,5,6-tetrahydro-2-(4-methoxyphenyl)-2H-thiopyran (1.22 g) as a colorless powder.

mp: 82-85°C

IR (KBr): 1610, 1514, 1252 cm^{-1}

NMR (DMSO- d_6 , δ): 1.35-1.65 (2H, m), 1.7-2.1 (4H, m), 2.56-2.64 (1H, m), 2.73-2.86 (1H, m), 3.72 (3H, s), 3.84 (1H, dd, $J=11.0$, 2.7Hz), 6.87 (2H, d, $J=8.7\text{Hz}$), 7.24 (2H, d, $J=8.7\text{Hz}$)

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{OS}$: C 69.19, H 7.74

Found: C 69.59, H 7.68

Preparation 1-2)

1.0M Solution of boron tribromide in dichloromethane (8.27 ml) was added dropwise to a stirred solution of 3,4,5,6-tetrahydro-2-(4-methoxyphenyl)-2H-thiopyran (718 mg) in dichloromethane (10 ml) under ice cooling and the

resulting mixture was stirred for 3 hours while the temperature was allowed to rise to room temperature. The reaction mixture was evaporated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: toluene - ethyl acetate) over silica gel (15.4 g) to afford 3,4,5,6-tetrahydro-2-(4-hydroxyphenyl)-2H-thiopyran (600 mg) as a colorless powder.

mp: 138-140.5°C

IR (KBr): 3421 (br), 1241 cm^{-1}

NMR (DMSO-d_6 , δ): 1.35-1.65 (2H, m), 1.7-2.05 (4H, m), 2.58 (1H, br d, $J=13.3\text{Hz}$), 2.71-2.85 (1H, m), 3.78 (1H, dd, $J=10.8, 2.5\text{Hz}$), 6.68 (2H, d, $J=8.5\text{Hz}$), 7.11 (2H, d, $J=8.5\text{Hz}$), 9.32 (1H, s)

Preparation 1-3)

A mixture of 3,4,5,6-tetrahydro-2-(4-hydroxyphenyl)-2H-thiopyran (578 mg), 4-bromochlorobenzene (683 mg), 8-hydroxyquinoline (17.3 mg), potassium carbonate (247 mg), and copper (I) chloride (11.8 mg) in 1,3-dimethyl-2-imidazolidinone (1.73 g) was stirred at 150°C under a nitrogen atmosphere for 21 hours and cooled to room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with a 1N aqueous solution of sodium hydroxide and brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was chromatographed (eluent: n-hexane-toluene) over silica gel to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (417 mg) as a colorless powder.

mp: 69.5-70.5°C

IR (KBr): 1274 cm^{-1}

NMR (CDCl_3 , δ): 1.45-1.77 (2H, m), 1.83-2.2 (4H, m), 2.66 (1H, m), 2.81-2.95 (1H, m), 3.84 (1H, dd,

J=11.6, 2.6Hz), 6.88-6.97 (4H, m), 7.23-7.36 (4H, m)

Preparation 1-4)

An aqueous solution (23 ml) of OXONE ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$,
5 1.82 g) was added dropwise to a suspension of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (600 mg) in methanol (23 ml) under ice cooling and the resulting mixture was stirred at room temperature for 17 hours. The reaction mixture was mixed with an aqueous solution (10 ml)
10 of sodium sulfite (746 mg) at room temperature, stirred at the same temperature for a while, and concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue
15 was washed with n-hexane to afford 2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (636 mg) as a colorless powder.

mp: 151.5-152°C

IR (KBr): 1313, 1247, 1120 cm^{-1}

20 NMR (CDCl_3 , δ): 1.65 (1H, m), 2.04-2.26 (4H, m), 2.37-2.56 (1H, m), 2.96-3.13 (1H, m), 3.24 (1H, m), 4.01 (1H, dd, J=12.8, 3.1Hz), 6.92-7.03 (4H, m), 7.28-7.42 (4H, m)

(+) APCI MS m/z: 336 ($\text{M}^+ + \text{H}$)

25

Preparation 1-5)

1.5M Solution of lithium diisopropylamide mono tetrahydrofuran in cyclohexane (1.47 ml) was added dropwise to a stirred suspension of 2-[4-(4-chlorophenoxy)phenyl]-
30 3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (621 mg) in tetrahydrofuran (9 ml) under a nitrogen atmosphere and dry ice - acetone cooling and the resultant suspension was stirred under the same conditions for 25 minutes. A solution of allyl bromide (491 mg) in tetrahydrofuran (2.5
35 ml) was added dropwise therein and the resultant mixture was

stirred under the same conditions for 2 hours and 30 minutes.

After addition of a saturated aqueous solution of ammonium chloride under the same conditions, the reaction mixture was extracted with ethyl acetate. The extract was washed

5 successively with 1N hydrochloric acid, brine, and a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: toluene - ethyl acetate) over silica gel to afford 2-allyl-2-[4-(4-chlorophenoxy)phenyl]-
10 3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (419 mg) as a colorless oil.

IR (Film): 1639, 1311, 1243, 1126 cm^{-1}

NMR (CDCl_3 , δ): 1.81-1.86 (2H, m), 2.09-2.21 (3H, m),
2.53-2.68 (1H, m), 2.86-3.09 (2H, m), 3.17-3.35
15 (2H, m), 5.02-5.09 (1H, m), 5.14-5.31 (2H, m),
6.94-7.05 (4H, m), 7.31 (2H, d, $J=9.0\text{Hz}$), 7.61 (2H,
d, $J=9.0\text{Hz}$)

(+) API-ES MS m/z : 399 and 401 ($\text{M}^+ + \text{Na}$)

20 Preparation 1-6)

1.5M Solution of lithium diisopropylamide mono tetrahydrofuran in cyclohexane (0.34 ml) was added dropwise to a stirred solution of 2-allyl-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-
25 dioxide (162 mg) in tetrahydrofuran (2.5 ml) under a nitrogen atmosphere and dry ice - acetone cooling and the resultant solution was stirred under the same conditions for 35 minutes. A solution of methyl iodide (134 mg) in tetrahydrofuran (0.5 ml) was added dropwise therein and the
30 resultant mixture was stirred under the same condition for 1 hour and 20 minutes. After addition of a saturated aqueous solution of ammonium chloride under the same conditions, the reaction mixture was extracted with ethyl acetate. The extract was washed successively with 1N hydrochloric acid
35 and brine, dried over sodium sulfate, and evaporated in

vacuo. The residue was chromatographed (eluent: toluene - ethyl acetate) over silica gel (8.1 g) to afford 2-allyl-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-6-methyl-2H-thiopyran 1,1-dioxide (78 mg) as a paste.

- 5 IR (KBr): 1639, 1284, 1244, 1126 cm^{-1}
NMR (CDCl_3 , δ): 1.38 (3H, d, $J=6.7\text{Hz}$), 1.82-2.25 (5H, m), 2.61 (1H, m), 2.99 (1H, dd, $J=14.3, 7.7\text{Hz}$), 3.32-3.39 (2H, m), 5.02-5.08 (1H, m), 5.16-5.29 (2H, m), 6.95-7.03 (4H, m), 7.28-7.33 (2H, m),
10 7.57-7.64 (2H, m)
(+) APCI MS m/z : 391 and 393 ($M^+ + H$)

Preparation 2

- 2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (148 mg) was prepared from 3,4,5,6-tetrahydro-2-(4-hydroxyphenyl)-2H-thiopyran (292 mg) and 4-chloroiodobenzene (430 mg) in a similar manner to that of Preparation 1-3).

mp: 69.5-70.5°C

Preparation 3

- 2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (97 mg) was prepared from tetrahydro-2H-thiopyran (510 mg) and 4-bromo-4'-chlorodiphenyl ether (2.12 g) in a similar manner to that of Preparation 1-1).

mp: 69.5-70.5°C

Preparation 4-1)

- 5-Chlorovaleryl chloride (17.1 g) was added dropwise to a stirred suspension of aluminum chloride (14.7 g) in dichloromethane (125 ml) under a nitrogen atmosphere and ice cooling over 5 minutes and the resulting solution was stirred under the same conditions for 10 minutes, then therein a solution of 4-chlorodiphenyl ether (20.5 g) in dichloromethane (115 ml) was added dropwise over 20 minutes.

The resulting mixture was stirred under the same conditions for 1 hour and 15 minutes, and poured into a mixture of 7% hydrochloric acid and ice. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The oily residue was powdered from n-hexane to afford 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (30.9 g) as a colorless powder.

mp: 59.5-60.5°C

IR (KBr): 1672, 1250 cm^{-1}

10 NMR (CDCl_3 , δ): 1.85-1.91 (4H, m), 2.94-3.02 (2H, m), 3.55-3.62 (2H, m), 6.96-7.05 (4H, m), 7.36 (2H, d, $J=9.0\text{Hz}$), 7.95 (2H, d, $J=8.9\text{Hz}$)
(+) API-ES MS m/z: 345, 347 and 349 ($\text{M}^+ + \text{Na}$)

15 Preparation 4-2)

A solution of sodium borohydride (2.16 g) in water (59 ml) was added dropwise to a stirred suspension of 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (30.8 g) and sodium bicarbonate (9.61 g) in ethanol (480 ml) under a nitrogen atmosphere at room temperature over 10 minutes and the resulting mixture was stirred under the same conditions for 3 hours. After removal of ethanol, the reaction mixture was acidified with 3N hydrochloric acid (70 ml) and extracted with toluene. The extract was washed successively with water, a saturated aqueous solution of sodium bicarbonate, and brine, dried over sodium sulfate, and evaporated in vacuo to afford 4-(5-chloro-1-hydroxypentyl)-4'-chlorodiphenyl ether (31.1 g) as a yellow oil.

IR (Film): 3383 (br), 1242 cm^{-1}

30 NMR (CDCl_3 , δ): 1.43-1.89 (7H, m), 3.53 (2H, t, $J=6.6\text{Hz}$), 4.67 (1H, m), 6.89-7.01 (4H, m), 7.24-7.34 (4H, m)
(+) API-ES MS m/z: 347, 349 and 351 ($\text{M}^+ + \text{Na}$), 311 and 313 ($\text{M}^+ - \text{HCl} + \text{Na}$)

35

Preparation 4-3)

Thionyl chloride (31.2 g) was added dropwise to a stirred solution of 4-(5-chloro-1-hydroxypentyl)-4'-chlorodiphenyl ether (31.0 g) in chloroform (383 ml) under ice cooling and the resulting solution was stirred under reflux for 4 hours. The reaction mixture was cooled to room temperature and evaporated in vacuo. The residue was partitioned between toluene and water. The organic layer was separated, washed with a saturated aqueous solution of sodium bicarbonate (twice) and brine, dried over sodium sulfate, and evaporated in vacuo to afford 4-chloro-4'-(1,5-dichloropentyl)diphenyl ether (33.7 g) as a pale brown oil.

IR (Film): 1242 cm^{-1}

NMR (CDCl_3 , δ): 1.47-1.85 (4H, m), 2.02-2.19 (2H, m), 3.53 (2H, t, $J=6.5\text{Hz}$), 4.85 (1H, dd, $J=7.9, 6.6\text{Hz}$), 6.91-7.00 (4H, m), 7.27-7.38 (4H, m)

Preparation 4-4)

Sodium sulfide nonahydrate (21.8 g) was added gradually to a stirred solution of 4-chloro-4'-(1,5-dichloropentyl)-diphenyl ether (24.0 g) in N,N-dimethylformamide (DMF, 240 ml) under ice cooling and a nitrogen atmosphere, and the resulting mixture was stirred under the same conditions for 2 hours and at room temperature for 3 days, then the reaction mixture was filtered. The filtrate was concentrated in vacuo and partitioned between water and toluene. The organic layer was separated, washed twice with brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was chromatographed (eluent: n-hexane - toluene) over silica gel to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (13.8 g) as a colorless powder.

mp: 69.5-70.5°C

Preparation 5-1)

5-(4-Chlorophenyl)-2-(5-chlorovaleryl)thiophene (3.75 g) was obtained in a similar manner to that of Preparation 4-1).

5 NMR (CDCl₃, δ): 1.86-1.95 (4H, m), 2.95 (2H, dd, J=6.9, 6.9Hz), 3.59 (2H, dd, J=6.9, 6.9Hz), 7.30 (1H, d, J=3.9Hz), 7.39 (2H, d, J=8.4Hz), 7.58 (2H, d, J=8.4Hz), 7.67 (1H, d, J=3.9Hz)

Preparation 5-2)

10 Ethyl 7-chloro-3-[5-(4-chlorophenyl)-2-thienyl]hept-2-enoate (4.2 g) was obtained in a similar manner to that of Preparation 8-2).

15 NMR (CDCl₃, δ): 1.21-1.34 (3H, m), 1.61-1.93 (4H, m), 2.53-2.57 (1H, m), 3.06-3.11 (1H, m), 3.52-3.60 (2H, m), 4.12-4.23 (2H, m), 5.88 (0.5H, s), 6.23 (0.5H, s), 7.21-7.34 (4H, m), 7.51-7.53 (2H, m)

Preparation 6-1)

20 Potassium tert-butoxide (1.34 g) was gradually added to a stirred solution of 4-chloro-4'-(1,5-dichloropentyl)-diphenyl ether (3.44 g) and thiobenzoic acid (1.66 g) in N,N-dimethylformamide (48 ml) under ice cooling and a nitrogen atmosphere over 5 minutes, and the resulting mixture was stirred at the same temperature for 2 hours and
25 at room temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate and an aqueous solution of sodium bicarbonate. The organic layer was separated, washed with a saturated aqueous solution of sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated in vacuo.
30 The oily residue (4.63 g) was chromatographed (eluent: n-hexane - toluene) over silica gel to afford 4-(1-benzoylthio-5-chloropentyl)-4'-chlorodiphenyl ether (1.16 g) as a pink oil.

IR (Film): 1660, 1242 cm⁻¹

35 NMR (CDCl₃, δ): 1.36-1.65 (2H, m), 1.75-1.90 (2H,

m), 1.99-2.12 (2H, m), 3.52 (2H, t, J=6.6Hz), 4.77 (1H, t, J=7.8Hz), 6.90-6.98 (4H, m), 7.25-7.57 (7H, m), 7.90-7.96 (2H, m)

(+) API-ES MS m/z: 467, 469 and 471 (M^+Na)

5

Preparation 6-2)

28% Solution of sodium methoxide in methanol (96.5 mg) was added dropwise to a stirred solution of 4-(1-benzoylthio-5-chloropentyl)-4'-chlorodiphenyl ether (223 mg) in methanol (1.1 ml) and acetonitrile (1.1 ml) under ice cooling and the resulting mixture was stirred at the same temperature for 2 hours, then additional 28% solution of sodium methoxide in methanol (96.5 mg), methanol (1.0 ml) and sodium iodide (7.5 mg) were added therein and the mixture was stirred at room temperature for 15 hours. The reaction mixture was acidified with 3N hydrochloric acid (0.5 ml) under ice cooling. The acidic mixture was extracted with toluene. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue (197 mg) was chromatographed (eluent: n-hexane - toluene) over silica gel (3.9 g) to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran (114 mg) as a colorless powder.

mp: 69.5-70.5°C

25

Preparation 7-1)

4-(4-Chlorobutyl)-4'-chlorodiphenyl ether (6.12 g) was prepared from 4-chlorobutyl chloride (3.10 g) and 4-chlorodiphenyl ether (4.09 g) in a similar manner to that of Preparation 4-1).

IR (Film): 1680, 1250 cm^{-1}

NMR (CDCl_3 , δ): 2.22 (2H, m), 3.14 (2H, t, J=7.0Hz), 3.68 (2H, t, J=6.2Hz), 6.96-7.05 (4H, m), 7.31-7.40 (2H, m), 7.93-8.01 (2H, m)

35

Preparation 7-2)

4-(4-Chloro-1-hydroxybutyl)-4'-chlorodiphenyl ether (6.14 g) was prepared in a similar manner to that of Preparation 4-2).

- 5 NMR (CDCl₃, δ): 1.76-2.01 (4H, m), 3.51-3.64 (2H, m),
4.70 (1H, m), 6.90-7.00 (4H, m), 7.24-7.34 (4H, m)
(+) API-ES MS m/z: 333, 335 and 337 (M⁺+Na)

Preparation 7-3)

- 10 4-Chloro-4'-(1,4-dichlorobutyl)diphenyl ether (5.75 g) was prepared in a similar manner to that of Preparation 4-3).

IR (Film): 1244 cm⁻¹

- NMR (CDCl₃, δ): 1.72-2.30 (4H, m), 3.57 (2H, t,
J=6.4Hz), 4.88 (1H, t, J=7.2Hz), 6.89-7.00 (4H, m),
15 7.24-7.39 (4H, m)
(+) API-ES MS m/z: 293 and 295 (M⁺-Cl)

Preparation 7-4)

- 20 2-[4-(4-Chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene (3.63 g) was prepared in a similar manner to that of Preparation 4-4).

IR (Film): 1238 cm⁻¹

- NMR (CDCl₃, δ): 1.87-2.02 (2H, m), 2.23-2.44 (2H, m),
2.99-3.17 (2H, m), 4.50 (1H, dd, J=8.4, 6.0Hz),
25 6.88-6.97 (4H, m), 7.23-7.31 (2H, m), 7.38 (2H, d,
J=8.5Hz)

Preparation 7-5)

- 30 2-[4-(4-Chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene 1,1-dioxide (3.05 g) was prepared in a similar manner to that of Preparation 1-4).

mp: 74.5-78.5°C

IR (Film): 1315, 1234, 1169, 1126 cm⁻¹

- NMR (CDCl₃, δ): 2.18-2.55 (4H, m), 3.12-3.36 (2H, m),
35 4.14 (1H, dd, J=11.7, 7.3Hz), 6.92-7.05 (4H, m),

7.28-7.39 (4H, m)

(+) APCI MS m/z: 323 and 325 ($M^+ + H$)

Preparation 8-1)

- 5 To a suspension of aluminum chloride (3.58 g) in methylene chloride (20 ml) was added a solution of 5-chlorovaleryl chloride (4.17 g) in methylene chloride (5 ml) dropwise at 0°C. After being stirred for 30 minutes at the same temperature, a solution of 4-chlorodiphenyl ether
- 10 (6 g) in methylene chloride (5 ml) was added therein and the mixture was stirred under ice-bath cooling for 2 hours. After 4N hydrochloric acid was added carefully to decompose excess aluminum chloride, the organic layer was separated and the aqueous layer was extracted with chloroform (20 ml x
- 15 2). The combined organic layer was washed with water and brine, and concentrated under reduced pressure. The resulting residue was washed with hexane to give 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (6.89 g) as a slightly yellow solid.
- 20 NMR (DMSO- d_6 , δ): 1.84-1.95 (4H, m), 2.99 (2H, t, $J=7\text{Hz}$), 3.42 (2H, t, $J=7\text{Hz}$), 6.99 (2H, d, $J=9\text{Hz}$), 7.00 (2H, d, $J=9\text{Hz}$), 7.37 (2H, d, $J=9\text{Hz}$), 7.96 (2H, d, $J=9\text{Hz}$)

25 Preparation 8-2)

- To a suspension of sodium hydride (60% oil dispersion, 3.14 g) in tetrahydrofuran (160 ml) was added a solution of triethyl phosphonoacetate (5.23 ml) in tetrahydrofuran (20 ml) at 0°C. After being stirred 30 minutes at the same
- 30 temperature, a solution of 4-(5-chlorovaleryl)-4'-chlorodiphenyl ether (48 g) in tetrahydrofuran (60 ml) was added therein, and the reaction mixture was refluxed overnight. The mixture was cooled to room temperature, poured into water, and concentrated under reduced pressure.
- 35 The residue was extracted with ethyl acetate (200 ml x 3).

The combined extract was washed with brine, dried over magnesium sulfate and concentrated to give ethyl 7-chloro-3-[4-(4-chlorophenoxy)phenyl]hept-2-enoate (E:Z = 1:1 mixture) (67.4 g) as a yellow oil.

5 NMR (CDCl₃, δ): 1.14 (1.5H, t, J=7Hz), 1.26 (1.5H, t, J=7Hz), 1.29-1.40 (2H, m), 1.50-1.67 (2H, m), 1.74-1.89 (2H, m), 2.45 (1.5H, t, J=7Hz), 3.09 (1.5H, t, J=7Hz), 3.51 (1H, t, J=7Hz), 3.53 (1H, t, J=7Hz), 4.03 (1H, q, J=7Hz), 4.14 (1H, q, J=7Hz),
10 5.89 (0.5H, s), 6.04 (0.5H, s), 6.90-7.01 (4H, m), 7.14 (2H, d, J=8Hz), 7.28 (1H, d, J=8Hz), 7.30 (1H, d, J=8Hz), 7.42 (2H, d, J=8Hz)

Preparation 8-3)

15 A solution of sodium iodide (128 g) and ethyl 7-chloro-3-[4-(4-chlorophenoxy)phenyl]hept-2-enoate (67.4 g) in acetone (200 ml) was refluxed for 24 hours. The resulting mixture was poured into water (300 ml) and extract with ethyl acetate (100 ml x 2). The combined organic layer was
20 washed with water and brine, and dried over magnesium sulfate to give ethyl 3-[4-(4-chlorophenoxy)phenyl]-7-iodohept-2-enoate (67.8 g) (E:Z = 1:1 mixture) as a yellow oil.

NMR (CDCl₃, δ): 1.14 (1.5H, t, J=7Hz), 1.26 (1.5H, t, J=7Hz), 1.29-1.37 (2H, m), 1.46-1.62 (2H, m),
25 1.78-1.94 (2H, m), 2.44 (1.5H, t, J=7Hz), 3.12 (1.5H, t, J=7Hz), 3.18 (3H, t, J=7Hz), 4.04 (1H, q, J=7Hz), 4.20 (1H, q, J=7Hz), 5.88 (0.5H, s), 6.04 (0.5H, s), 6.89-7.00 (4H, m), 7.14 (2H, d, J=8Hz), 7.26-7.36 (3H, m), 7.42 (2H, d, J=8Hz)

30

Preparation 8-4)

A mixture of ethyl 3-[4-(4-chlorophenoxy)phenyl]-7-iodohept-2-enoate (59.8 g) and thiourea (9.39 g) in ethanol (123 ml) was refluxed for 24 hours. The resulting mixture
35 was cooled and evaporated to give ethyl 7-amidinothio-3-[4-

(4-chlorophenoxy)phenyl]hept-2-enoate hydroiodide (70.2 g)
(E:Z = 1:1 mixture) as slightly yellow oil.

NMR (DMSO-d₆, δ): 1.05 (1.5H, t, J=7Hz), 1.24 (1.5H,
t, J=7Hz), 1.33-1.68 (4H, m), 2.48 (1H, t, J=7Hz),
3.05-3.16 (3H, m), 3.96 (1H, q, J=7Hz), 4.12 (1H,
q, J=7Hz), 5.93 (0.5H, s), 6.07 (0.5H, s), 6.96-
7.13 (4H, m), 7.20 (1H, d, J=8Hz), 7.46 (1H, d,
J=8Hz), 7.48 (1H, d, J=8Hz), 7.60 (1H, d, J=8Hz)

MS (ES-) m/z: 433 (M-H)

Preparation 9-1)

4-(5-Chlorovaleryl)-4'-fluorodiphenyl ether (3.86 g)
was obtained in a similar manner to that of Preparation 4-1).

NMR (CDCl₃, δ): 1.81-1.92 (4H, m), 2.97 (2H, dd, J=7,
7Hz), 3.53-3.6 (2H, m), 6.94-7.12 (6H, m), 7.92-
7.95 (2H, m)

Preparation 9-2)

Ethyl 7-chloro-3-[4-(4-fluorophenoxy)phenyl]hept-2-
enoate (1.90 g) was obtained in a similar manner to that of
Preparation 8-2).

NMR (CDCl₃, δ): 1.31 (3H, dd, J=7, 7Hz), 1.54-1.64
(2H, m), 1.78-1.88 (2H, m), 3.12 (2H, dd, J=7.5,
7.5Hz), 3.53 (2H, dd, J=7, 7Hz), 4.20 (2H, ddd,
J=7, 7, 7Hz), 6.03 (1H, s), 6.93-7.09 (6H, m),
7.39-7.42 (2H, m)

Preparation 10-1)

4-(5-Chlorovaleryl)-4'-bromodiphenyl ether (6.71 g) was
obtained in a similar manner to that of Preparation 4-1).

NMR (CDCl₃, δ): 1.82-1.94 (4H, m), 2.99 (2H, t,
J=6.5Hz), 3.60 (2H, t, J=6.5Hz), 6.95 (2H, d,
J=9Hz), 7.00 (2H, d, J=9Hz), 7.51 (2H, d, J=9Hz),
7.95 (2H, d, J=9Hz)

Preparation 10-2

Ethyl 3-[4-(4-bromophenoxy)phenyl]-7-chlorohept-2-enoate (7.55 g) was obtained in a similar manner to that of Preparation 8-2).

5 NMR (CDCl₃, δ): 1.14 (1.5H, t, J=7Hz), 1.21-1.39
 (1.5H, m), 1.49-1.65 (2H, m), 1.74-1.88 (2H, m),
 2.47 (1H, t, J=7Hz), 3.12 (1H, t, J=7Hz), 3.47-
 3.56 (2H, m), 4.03 (1H, q, J=7Hz), 4.20 (1H, q,
 J=7Hz), 5.89 (0.5H, s), 6.04 (0.5H, s), 6.86-6.99
10 (4H, m), 7.39-7.50 (4H, m)

Preparation 10-3)

Ethyl 3-[4-(4-bromophenoxy)phenyl]-7-iodohept-2-enoate (7.85 g) was obtained in a similar manner to that of

15 Preparation 8-3).

 NMR (CDCl₃, δ): 1.14 (1.5H, t, J=7Hz), 1.21-1.39
 (1.5H, m), 1.49-1.65 (2H, m), 1.74-1.88 (2H, m),
 2.47 (1H, t, J=7Hz), 3.12 (1H, t, J=7Hz), 3.47-
 3.56 (2H, m), 4.03 (1H, q, J=7Hz), 4.20 (1H, q,
20 J=7Hz), 5.89 (0.5H, s), 6.04 (0.5H, s), 6.86-6.99
 (4H, m), 7.39-7.50 (4H, m)

Preparation 10-4)

25 Ethyl 7-amidinothio-3-[4-(4-bromophenoxy)phenyl]hept-2-
 enoate hydroiodide (10.4 g) was obtained in a similar manner
 to that of Preparation 8-4).

 NMR (DMSO-d₆, δ): 1.06 (1.5H, t, J=7Hz), 1.24 (1.5H,
 t, J=7Hz), 1.35-1.52 (2H, m), 1.54-1.75 (2H, m),
 3.06-3.17 (2H, m), 3.39-3.49 (2H, m), 3.94 (1H, q,
30 J=7Hz), 4.15 (1H, q, J=7Hz), 5.94 (0.5H, s), 6.07
 (0.5H, s), 6.96-7.11 (4H, m), 7.56-7.64 (4H, m),
 9.01-9.15 (4H, m)

MS (ESI+) m/z: 479, 563 (+TFA)

35 Preparation 11-1)

Methyl 4-(5-chlorovaleryl)phenyl ether (8.77 g) was obtained in a similar manner to that of Preparation 4-1).

NMR (CDCl₃, δ): 1.84-1.94 (4H, m), 2.97 (2H, t, J=7Hz), 3.59 (2H, t, J=6.5Hz), 3.88 (3H, s), 6.94 (2H, d, J=9Hz), 7.95 (2H, d, J=9Hz)

Preparation 11-2)

To a stirred solution of lithium diisopropylamide in tetrahydrofuran (prepared from diisopropylamine (2.32 g) and n-butyl lithium (14.3 ml, 1.6M in n-hexane) in tetrahydrofuran (14 ml) was added dropwise ethyl acetate (2.80 g) while maintaining -60°C on a dry-ice acetone bath. The mixture was stirred for 1 hour at -60°C and quenched by addition of saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate. The obtained organic phase was washed with saturated aqueous ammonium chloride three times and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluted with 5 to 10% ethyl acetate in n-hexane) to give ethyl 7-chloro-3-hydroxy-3-(4-methoxyphenyl)-heptanoate (3.56 g) as an oil.

NMR (CDCl₃, δ): 1.12 (3H, t, J=7.5Hz), 1.16-1.30 (1H, m), 1.39-1.56 (1H, m), 1.62-1.82 (4H, m), 2.77 (1H, d, J=16Hz), 2.94 (1H, d, J=16Hz), 3.45 (2H, t, J=6.5Hz), 3.80 (3H, s), 4.04 (2H, q, J=7.5Hz), 4.38 (1H, s), 6.86 (2H, d, J=9Hz), 7.31 (2H, d, J=9Hz)

Preparation 11-3)

A mixture of ethyl 7-chloro-3-hydroxy-3-(4-methoxyphenyl)heptanoate (3.55 g), potassium thioacetate (1.42 g) and catalytic amount of tetrabutyl ammonium iodide (n-Bu₄NI) (150 mg) in N,N-dimethylformamide (30 ml) was stirred for 6 hours at room temperature. The mixture was poured into saturated aqueous ammonium chloride and

extracted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride three times and brine, dried over sodium sulfate and evaporated in vacuo to give ethyl 7-acetylthio-3-hydroxy-3-(4-

5 methoxyphenyl)heptanoate (3.61 g) as an oil.

NMR (CDCl₃, δ): 1.12 (3H, t, J=7Hz), 1.33-1.55 (4H, m), 1.66-1.80 (2H, m), 2.30 (3H, s), 2.72-2.81 (3H, m), 2.93 (1H, d, J=15.5Hz), 3.80 (3H, s), 4.03 (2H, q, J=7Hz), 4.36 (1H, s), 6.85 (2H, d, J=9Hz), 7.30 (2H, d, J=9Hz)

Preparation 11-4)

A mixture of ethyl 7-acetylthio-3-hydroxy-3-(4-methoxyphenyl)heptanoate (3.60 g) and potassium carbonate (1.40 g) in ethanol (54 ml) was stirred for 6 hours at room temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and 1% aqueous citric acid.

The separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo to give ethyl 3-hydroxy-3-(4-methoxyphenyl)-7-mercaptoheptanoate (3.01 g) as an oil.

NMR (CDCl₃, δ): 1.12 (3H, t, J=7.5Hz), 1.26 (1H, t, J=7.5Hz), 1.35-1.60 (4H, m), 1.65-1.82 (2H, m), 2.40-2.57 (2H, m), 2.77 (1H, d, J=16Hz), 2.94 (1H, d, J=16Hz), 3.80 (3H, s), 4.04 (2H, q, J=7.5Hz), 4.36 (1H, s), 6.86 (2H, d, J=9Hz), 7.30 (2H, d, J=9Hz)

Preparation 12-1)

5-(4-Fluorophenyl)-2-(5-chlorovaleryl)thiophene (2.03 g) was obtained in a similar manner to that of Preparation 4-1).

NMR (CDCl₃, δ): 1.79-1.99 (4H, m), 2.95 (2H, t, J=7Hz), 3.59 (2H, t, J=7Hz), 7.12 (2H, dd, J=8, 8Hz), 7.59-7.68 (4H, m)

Preparation 12-2)

Ethyl 7-chloro-3-[5-(4-fluorophenyl)-2-thienyl]hept-2-enoate (1.71 g) (E:Z = 1:1 mixture) was obtained in a similar manner to that of Preparation 8-2).

NMR (CDCl₃, δ): 1.24 (1.5H, t), 1.37 (1.5H, t), 1.63-1.98 (4H, m), 2.56 (0.5H, t, J=7Hz), 2.87-3.00 (1H, m), 3.08 (0.5H, t, J=7Hz), 3.53 (1H, t, J=7Hz), 3.61 (1H, t, J=7Hz), 4.10-4.24 (2H, m), 5.87 (0.5H, s), 6.22 (0.5H, s), 7.04-7.31 (3H, m), 7.55-7.69 (3H, m)

Preparation 12-3)

Ethyl 3-[5-(4-fluorophenyl)-2-thienyl]-7-iodohept-2-enoate (1.94 g) was obtained in a similar manner to that of Preparation 8-3).

NMR (CDCl₃, δ): 1.06 (1.5H, t, J=7Hz), 1.32 (1.5H, t, J=7Hz), 1.67-2.08 (4H, m), 3.24 (2H, t, J=7Hz), 4.18 (2H, q, J=7Hz), 6.22 (1H, s), 6.92-7.30 (4H, m), 7.48-7.60 (2H, m)

Preparation 12-4)

Ethyl 7-amidinothio-3-[5-(4-fluorophenyl)-2-thienyl]hept-2-enoate hydroiodide (1.57 g) was obtained in a similar manner to that of Preparation 8-4).

NMR (CDCl₃, δ): 1.05 (3H, t, J=7Hz), 1.57-1.82 (4H, m), 3.18 (2H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 4.36 (2H, t, J=7Hz), 6.19 (1H, s), 7.24-7.69 (6H, m)

MS (ESI+) m/z = 407 (M+H)

Preparation 13-1)

4-(5-Chlorovaleryl)biphenyl (1.35 g) was obtained in a similar manner to that of Preparation 4-1).

NMR (CDCl₃, δ): 1.90-1.93 (4H, m), 3.06 (2H, dd, J=6, 6Hz), 3.61 (2H, dd, J=7, 7Hz), 7.40-7.50 (3H, m),

7.63 (2H, d, J=8Hz), 7.69 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

Preparation 13-2)

5 Ethyl 3-(4-biphenyl)-7-chlorohept-2-enoate (1 g) was obtained in a similar manner to that of Preparation 8-2).

NMR (CDCl₃, δ): 1.10 (1.5H, dd, J=7, 7Hz), 1.33 (1.5H, dd, J=7, 7Hz), 1.55-1.68 (1H, m), 1.76-1.90 (1H, m), 2.51 (1H, dd, J=7.5, 7.5Hz), 3.18 (1H, dd, J=7.5, 7.5Hz), 3.52 (1H, dd, J=6.5, 6.5Hz), 3.54 (1H, dd, J=6.5, 6.5Hz), 4.02 (1H, ddd, J=7, 7, 7Hz), 4.22 (1H, ddd, J=7, 7, 7Hz), 5.92 (0.5H, s), 6.13 (0.5H, s), 7.24-7.65 (9H, m)

15 Preparation 14-1)

4'-Chloro-4-(5-chlorovaleryl)biphenyl (3.29 g) was obtained in a similar manner to that of Preparation 4-1).

NMR (CDCl₃, δ): 1.90-1.93 (4H, m), 3.05 (2H, dd, J=6, 6Hz), 3.60 (2H, dd, J=6, 6Hz), 7.44 (2H, d, J=8Hz), 7.56 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

Preparation 14-2)

Ethyl 7-chloro-3-(4'-chloro-4-biphenyl)hept-2-enoate (0.70 g) was obtained in a similar manner to that of Preparation 8-2).

NMR (CDCl₃, δ): 1.11 (1.5H, dd, J=7, 7Hz), 1.32 (1.5H, dd, J=7, 7Hz), 1.50-1.58 (1H, m), 1.58-1.65 (1H, m), 2.49 (1H, dd, J=7, 7Hz), 3.17 (1H, dd, J=7, 7Hz), 3.50 (1H, dd, J=6, 6Hz), 3.54 (1H, dd, J=6, 6Hz), 4.01 (1H, ddd, J=7, 7, 7Hz), 4.22 (1H, ddd, J=7, 7, 7Hz), 5.93 (0.5H, s), 6.12 (0.5H, s), 7.40-7.58 (8H, m)

35 Preparation 15-1)

4'-Bromo-4-(5-chlorovaleryl)biphenyl (1.97 g) was obtained in a similar manner to that of Preparation 4-1).

5 NMR (CDCl₃, δ): 1.90-1.93 (4H, m), 3.05 (2H, dd, J=7, 7Hz), 3.60 (2H, dd, J=6, 6Hz), 7.49 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 8.03 (2H, d, J=8Hz)

Preparation 15-2)

10 Ethyl 7-chloro-3-(4'-bromo-4-biphenylyl)hept-2-enoate (0.64 g) was obtained in a similar manner to that of Preparation 8-2).

15 NMR (CDCl₃, δ): 1.11 (1.5H, dd, J=7, 7Hz), 1.33 (1.5H, dd, J=7, 7Hz), 1.52-1.67 (2H, m), 1.75-1.89 (2H, m), 2.50 (1H, dd, J=7, 7Hz), 3.17 (1H, dd, J=8, 8Hz), 3.51 (1H, dd, J=7, 7Hz), 3.54 (1H, dd, J=7, 7Hz), 4.02 (1H, ddd, J=7, 7, 7Hz), 4.22 (1H, ddd, J=7, 7, 7Hz), 5.93 (0.5H, s), 6.11 (0.5H, s), 7.24-7.60 (8H, m)

20 Preparation 16-1)

4'-Fluoro-4-(5-chlorovaleryl)biphenyl (2.95 g) was obtained in a similar manner to that of Preparation 4-1).

25 NMR (CDCl₃, δ): 1.89-1.95 (4H, m), 3.05 (2H, dd, J=7, 7Hz), 3.60 (2H, dd, J=6, 6Hz), 7.13-7.19 (2H, m), 7.57-7.65 (2H, m), 8.03 (2H, d, J=8.4Hz)

Preparation 16-2)

30 Ethyl 7-chloro-3-(4'-fluoro-4-biphenylyl)hept-2-enoate (1.07 g) was obtained in a similar manner to that of Preparation 8-2).

35 NMR (CDCl₃, δ): 1.33 (3H, dd, J=7, 7Hz), 1.59-1.67 (2H, m), 1.81-1.90 (2H, m), 3.17 (2H, dd, J=7.5, 7.5Hz), 3.54 (2H, dd, J=7, 7Hz), 4.22 (2H, ddd, J=7, 7, 7Hz), 6.12 (1H, s), 7.14 (2H, dd, J=8, 8Hz), 7.50-7.59 (6H, m)

Preparation 17)

Methyl 3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate
1,1-dioxide (844 mg) was obtained in a similar manner to
5 that of Preparation 1-4).

mp: 78-82°C

NMR (CDCl₃, δ): 1.44-1.80 (3H, m), 1.83-1.96 (1H, m),
2.10-2.42 (2H, m), 2.72-2.85 (1H, m), 3.14-3.78
(1H, m), 5.57 (1H, dd, J=3, 8Hz), 3.82 (3H, s)

10 MS (ESI-) m/z: 191 (M-H)

Preparation 18)

To a solution of potassium ethyl malonate (16.7 g) in
acetonitrile (4 ml) was added triethylamine (15.1 g) and
15 magnesium chloride (11.1 g) at 0°C and the reaction mixture
was stirred at ambient temperature for 2.5 hours. To the
resulting slurry was added phenoxybenzoyl chloride (10.86 g)
[prepared from 4-phenoxybenzoic acid (10 g) and thionyl
chloride (20 ml)] dropwise over 25 minutes at 0°C and the
20 reaction mixture was stirred at ambient temperature for 5
hours. After the reaction mixture was concentrated in vacuo,
toluene and 13% aqueous hydrochloric acid (60 ml) was added
therein cautiously while keeping the temperature below 25°C.
The organic layer was washed with 13% aqueous hydrochloric
25 acid and concentrated in vacuo to give ethyl 3-oxo-3-(4-
phenoxyphenyl)propanoate as a yellow oil (14 g).

NMR (CDCl₃, δ): 1.27 (3H, t, J=7.0Hz), 3.95 (2H, s),
4.24 (2H, q, J=7.0Hz), 6.99 (2H, d, J=8.0Hz),
7.07 (2H, d, J=8.0Hz), 7.18 (1H, dd, J=8.0,
30 8.0Hz), 7.41 (2H, dd, J=8.0, 8.0Hz), 7.92 (2H, d,
J=8.0Hz)

MS (ESI-) m/z: 283.1 (M-H)

Preparation 19-1)

35 5-Bromo-2-(5-chlorovaleryl)thiophene (13.4 g) was

obtained in a similar manner to that of Preparation 4-1).

NMR (CDCl₃, δ): 1.86-1.91 (4H, m), 2.88 (2H, dd, J=6.9, 6.9Hz), 3.55 (2H, dd, J=6.6, 6.6Hz), 7.11 (1H, d, J=4.2Hz), 7.45 (1H, d, J=4.2Hz)

5

Preparation 19-2)

Ethyl 7-chloro-3-(5-bromo-2-thienyl)hept-2-enoate (12.5 g) was obtained in a similar manner to that of Preparation 8-2).

10 NMR (CDCl₃, δ): 1.22-1.59 (3H, m), 1.65-1.92 (4H, m), 3.01-3.06 (1H, m), 3.50-3.59 (2H, m), 4.10-4.23 (2H, m), 5.85 (0.5H, s), 6.09 (0.5Hz, s), 6.98-7.07 (2H, m)

15 Preparation 20-1)

tert-Butyl 7-chloro-3-hydroxy-3-(5-bromo-2-thienyl)heptanoate (244 g) was obtained in substantially the same manner as that of Preparation 11-2).

20 NMR (CDCl₃, δ): 1.36 (9H, s), 1.38-1.57 (2H, m), 1.68-1.80 (4H, m), 2.70 (1H, d, J=15.6Hz), 2.79 (1H, d, J=15.6Hz), 3.49 (2H, t, J=6.9Hz), 5.00 (1H, s), 6.59 (1H, d, J=3.9Hz), 6.89 (1H, d, J=3.9Hz)

Preparation 20-2)

25 tert-Butyl 7-acetylthio-3-hydroxy-3-(5-bromo-2-thienyl)heptanoate (267 g) was obtained in substantially the same manner as that of Preparation 11-3).

30 NMR (CDCl₃, δ): 1.35 (9H, s), 1.39-1.57 (4H, m), 1.66-1.80 (2H, m), 2.31 (3H, s), 2.67 (1H, d, J=15.9Hz), 2.76 (1H, d, J=15.9Hz), 2.82 (2H, t, J=7.5Hz), 4.96 (1H, s), 6.58 (1H, d, J=3.9Hz), 6.88 (1H, d, J=3.9Hz)

Preparation 20-3)

35 tert-Butyl 3-hydroxy-3-(5-bromo-2-thienyl)-7-

mercaptoheptanoate (277 g) was obtained in substantially the same manner as that of Preparation 11-4).

5 NMR (CDCl₃, δ): 1.30 (1H, t, J=7.8Hz), 1.31-1.39 (9H, m), 1.40-1.65 (4H, m), 1.67-1.83 (2H, m), 2.49 (2H, dd, J=7.8, 15Hz), 2.70 (1H, d, J=16H), 2.79 (1H, d, J=16Hz), 4.98 (1H, s), 6.59 (1H, d, J=4.2Hz), 6.89 (1H, d, J=4.2Hz)

Preparation 21-1)

10 To a solution of 4-bromophenol (300 mg) in acetone was added potassium carbonate (264 mg) and bromoacetic acid t-butyl ester (0.28 ml) at room temperature. After being stirred at the same temperature overnight, the reaction mixture was concentrated in vacuo. The resulting residue
15 was diluted with ethyl acetate, washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated in vacuo to give 4-bromophenoxy acetic acid t-butyl ester (450 mg) as an oil.

20 NMR (DMSO-d₆, δ): 1.42 (9H, s), 4.66 (2H, s), 6.88 (2H, d, J=4.5Hz), 7.45 (2H, d, J=4.5Hz)

Preparation 21-2)

To a solution of 4-bromophenoxyacetic acid t-butyl ester (4 g) in dichloromethane (10 ml) was added
25 trifluoroacetic acid (30 ml) at room temperature. After being stirred at the same temperature for 3 hours, the reaction mixture was concentrated in vacuo. The resulting residue was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated in
30 vacuo to give 4-bromophenoxy acetic acid (2.1 g) as a power.

NMR (DMSO-d₆, δ): 4.67 (2H, s), 6.89 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz)

MS (ESI-): 230 (M-H)

35 Preparation 21-3)

N-Ethyl-2-(4-bromophenoxy)acetamide (110 mg) was obtained in substantially the same manner as that of Example 32.

5 NMR (DMSO- d_6 , δ): 1.03 (3H, t, $J=7.2\text{Hz}$), 3.10-3.19 (2H, m), 4.45 (2H, s), 6.93 (2H, d, $J=9\text{Hz}$), 7.47 (2H, d, $J=9\text{Hz}$), 8.11 (1H, br)

Preparation 21-4)

10 4-(Ethylaminocarbonylmethoxy)benzeneboronic acid pinacol cyclic ester (130 mg) was obtained in substantially the same manner as that of Preparation 24-2).

The product was used for the next reaction without further purification.

15 Preparation 22

4-(*t*-Butyloxycarbonylmethoxy)benzeneboronic acid (200 mg) was obtained in substantially the same manner as that of Preparation 21-1).

20 NMR (DMSO- d_6 , δ): 1.42 (9H, s), 4.65 (2H, s), 6.84 (2H, d, $J=9.0\text{Hz}$), 7.71 (2H, d, $J=9.0\text{Hz}$), 7.88 (2H, s)

Preparation 23-1)

25 4-Chloro-1-(5-bromo-2-thienyl)butan-1-one (8.0 g) was obtained in substantially the same manner as that of Preparation 8-1).

NMR (CDCl₃, δ): 2.21 (2H, quintet, $J=7\text{Hz}$), 3.05 (2H, t, $J=7\text{Hz}$), 3.66 (2H, t, $J=7\text{Hz}$), 7.11 (1H, d, $J=4\text{Hz}$), 7.50 (1H, d, $J=4\text{Hz}$)

30 Preparation 23-2)

tert-Butyl 6-chloro-3-hydroxy-3-(5-bromo-2-thienyl)hexanoate (4.46 g) was obtained in substantially the same manner as that of Preparation 11-2).

NMR (CDCl₃, δ): 1.37 (9H, s), 1.64-1.80 (1H, m),

1.82-1.98 (3H, m), 2.70 (1H, d, J=16Hz), 2.80 (1H, d, J=16Hz), 3.48-3.55 (2H, m), 5.02 (1H, s), 6.61 (1H, d, J=4Hz), 6.90 (1H, d, J=4Hz)

5 Preparation 23-3)

tert-Butyl 6-acetylthio-3-hydroxy-3-(5-bromo-2-thienyl)hexanoate (4.77 g) was obtained in substantially the same manner as that of Preparation 11-3).

10 NMR (CDCl₃, δ): 1.36 (9H, s), 1.45-1.60 (1H, m),
1.62-1.94 (3H, m), 2.31 (3H, s), 2.68 (1H, d, J=16Hz), 2.77 (1H, d, J=16Hz), 2.85 (2H, t, J=7Hz), 4.98 (1H, s), 6.59 (1H, d, J=4Hz), 6.88 (1H, d, J=4Hz)

15 Preparation 23-4)

tert-Butyl 3-hydroxy-3-(5-bromo-2-thienyl)-6-mercaptohexanoate (4.0 g) was obtained in substantially the same manner as that of Preparation 11-4).

20 NMR (CDCl₃, δ): 1.30 (1H, t, J=8Hz), 1.36 (9H, s), 1.44-1.62 (1H, m), 1.66-1.93 (3H, m), 2.44-2.55 (2H, m), 2.70 (1H, d, J=16Hz), 2.79 (1H, d, J=16Hz), 4.99 (1H, s), 6.60 (1H, d, J=4Hz), 6.89 (1H, d, J=4Hz)

Preparation 24-1)

25 A mixture of 4-bromobenzaldehyde (5.00 g), tosylmethyl isocyanide (5.43 g) and potassium carbonate (5.60 g) in methanol (50 ml) was refluxed for 2 hours and concentrated. The residue was taken up between ethyl acetate and saturated aqueous ammonium hydrochloride. The separated organic layer
30 was washed with water and brine, dried over sodium sulfate and filtered. The filtrate was treated with silica gel and the obtained residue was triturated with n-hexane to give 5-(4-bromophenyl)oxazole (4.06 g) as a solid.

35 NMR (CDCl₃, δ): 7.37 (1H, s), 7.51-7.58 (4H, m),
7.93 (1H, s)

MS (ESI+): 224 (M+H)

Preparation 24-2)

A mixture of 5-(4-bromophenyl)oxazole (672 mg),
5 bis(pinacolato)diborane (762 mg) dichlorobis(triphenyl-
phosphine)palladium(II) (42.1 mg) and potassium acetate (883
mg) in dioxane (15 ml) was stirred for 14 hours at 80°C to
form 4-(5-oxazolyl)benzeneboronic acid pinacol cyclic ester.
After cooling to room temperature, the mixture was used to
10 next reaction without further purification.

Preparation 25

(4-(Methoxycarbonylaminomethyl)phenyl)boronic acid (70
mg) was obtained from (4-aminomethylphenyl)boronic acid
15 hydrochloride in a similar manner to that of Example 130.

NMR (DMSO-d₆, δ): 3.53 (3H, s), 4.18 (2H, d, J=7.5Hz),
7.20 (2H, d, J=8.5Hz), 7.66-7.75 (3H, m), 8.00 (2H,
s)

20 Preparation 26

(4-(Cyclopropylcarbonyloxy)phenyl)boronic acid (77 mg)
was obtained from (4-hydroxyphenyl)boronic acid in a similar
manner to that of Preparation 21-1).

NMR (DMSO-d₆, δ): 1.00-1.07 (4H, m), 1.85-1.94 (1H, m),
25 7.08 (2H, d, J=8.5Hz), 7.81 (2H, d, J=8.5Hz), 8.09
(2H, s)

Preparation 27

(4-(Ethoxycarbonylmethoxy)phenyl)boronic acid (100 mg)
30 was obtained in a similar manner to that of Preparation 21-
1).

NMR (DMSO-d₆, δ): 1.21 (3H, dd, J=7.2, 7.2Hz), 4.17 (2H,
ddd, J=7.2, 7.2, 7.2Hz), 4.78 (2H, s), 6.87 (2H, d,
J=8.5Hz), 7.72 (2H, d, J=8.5Hz), 7.88 (2H, s)

Preparation 28

(4-(Ethylcarbonylmethoxy)phenyl)boronic acid (95 mg) was obtained in a similar manner to that of Preparation 21-1).

5 NMR (DMSO- d_6 , δ): 0.97 (3H, dd, $J=7.2$, 7.2Hz), 2.49-2.54 (2H, m), 4.82 (2H, s), 6.84 (2H, d, $J=8.5$ Hz), 7.71 (2H, d, $J=8.5$ Hz), 7.87 (2H, s)

Preparation 29

10 (4-Cyclopropylaminocarbonylmethoxyphenyl)boronic acid (160 mg) was obtained in a similar manner to that of Example 32.

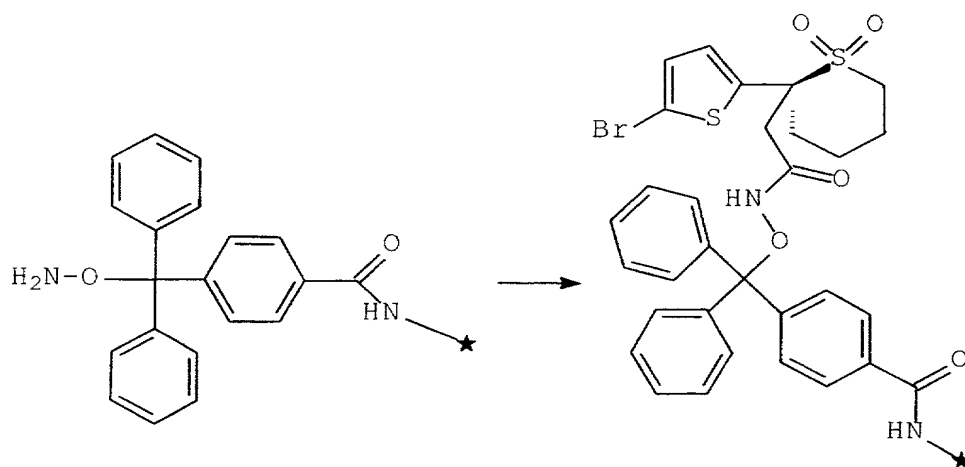
NMR (DMSO- d_6 , δ): 0.46-0.50 (2H, m), 0.61-0.64 (2H, m),
2.65-2.72 (1H, m), 4.43 (2H, s), 6.88 (2H, d,
15 $J=8.5$ Hz), 7.72 (2H, d, $J=8.5$ Hz), 7.88 (2H, s),
8.13 (1H, br)

Preparation 30

20

25

30



(a)

(b)

To a solution of (2S)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (4.24 g)
35 in N,N-dimethylformamide (60 ml) was added 1-hydroxy-

benztriazole (1.62 g) and diisopropylcarbodiimide (1.88 ml) at ambient temperature. After 1 minute, the solution was added to hydroxylamine trityl crowns (a) (14.4 $\mu\text{mol}/\text{crown} \times 100$), the reaction mixture was left overnight at ambient temperature. The crowns were washed with N,N-dimethylformamide, methanol and dichloromethane, successively and air dried to give (2S)-N-[2-[2-(5-bromo-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]-hydroxylamine trityl crowns (b) (10.0 $\mu\text{mol}/\text{crown} \times 100$).

10

Preparation 31-1)

To a suspension of 3-nitrophenylboronic acid (2.33 g) and tetrakis(triphenylphosphine)palladium (1.29 g) in degassed N,N-dimethylformamide (50 ml) was added a solution of sodium carbonate (8.5 g) in degassed water (20 ml) and (2S)-N-[2-[2-(5-bromo-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]hydroxylamine trityl crowns (202 μmol , 10.1 $\mu\text{mol}/\text{crown} \times 20$) in an atmosphere of nitrogen. After the resulting mixture was heated for 48 hours at 60°C, the crowns were washed with degassed N,N-dimethylformamide, a solution of sodium diethyldithiocarbamate (1.0 g) and diisopropylethylamine (1.0 ml) in N,N-dimethylformamide (200 ml), N,N-dimethylformamide, methyl sulfoxide, water, methanol and dichloromethane, successively to give (2S)-N-[2-[2-(5-(3-nitrophenyl)-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]hydroxylamine trityl crowns (202 μmol , 10.1 $\mu\text{mol}/\text{crown} \times 20$).

Preparation 31-2)

To a solution of 2M tin (II) chloride dihydrate (7.67 g) in N,N-dimethylformamide (17 ml) was added (2S)-N-[2-[2-(5-(3-nitrophenyl)-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]hydroxylamine trityl crowns (304 μmol , 13.2 $\mu\text{mol}/\text{crown} \times 23$). The reaction mixture was left

overnight at ambient temperature. The crowns were washed with N,N-dimethylformamide, water, methanol and dichloromethane, successively and air dried to give (2S)-N-[2-[2-(5-(3-aminophenyl)-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]hydroxylamine trityl crowns (13.2 μ mol/crown x 23).

The following compounds were obtained from 6-methyl-3-(trifluoromethanesulfonyloxy)pyridine in a similar manner to that of Preparation 24-2).

Preparation 32

6-Methylpyridine-3-boronic acid pinacol cyclic ester

Preparation 33

6-Methoxypyridine-3-boronic acid pinacol cyclic ester

Preparation 34

4-(5-Methyl-1,2,4-oxadiazol-3-yl)benzeneboronic acid pinacol cyclic ester

Preparation 35

5-(Methoxycarbonylamino)pyridine-3-boronic acid pinacol cyclic ester

Preparation 36

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(pinacolatoboryl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

Preparation 37

4-(Methylaminocarbonylmethyl)benzeneboronic acid pinacol cyclic ester

Preparation 38

2-(Methylaminocarbonyl)benzofuran-5-boronic acid
pinacol cyclic ester

Example 1

5 1.5M Lithium diisopropylamide mono tetrahydrofuran in
cyclohexane (0.28 ml) was added dropwise to a stirred
suspension of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-
tetrahydro-2H-thiopyran 1,1-dioxide (117 mg) in
tetrahydrofuran (2.4 ml) under dry ice - acetone cooling and
10 a nitrogen atmosphere, and the mixture was stirred under the
same conditions for 15 minutes, then a solution of
tert-butyl bromoacetate (75 mg) in tetrahydrofuran (0.2 ml)
was added dropwise therein and the resulting mixture was
stirred under the same conditions for 2 hours. A saturated
15 aqueous solution of ammonium chloride was added to the
stirred reaction mixture and the resulting mixture was
extracted with diethyl ether. The extract was washed with
brine, dried over sodium sulfate, and evaporated in vacuo.
The residue was chromatographed (eluent: toluene - ethyl
20 acetate) over silica gel to afford a mixture (86 mg) of
t-butyl 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetate 1,1-dioxide and the starting material.

A solution of trifluoroacetic acid (560 mg) and the
obtained mixture (79 mg) in dichloromethane (3.0 ml) was
25 allowed to stand at room temperature for 3 days and
evaporated in vacuo. The residue was dissolved in ethyl
acetate and extracted five times with a saturated aqueous
solution of sodium bicarbonate. The aqueous extracts were
combined, acidified with hydrochloric acid, and extracted
30 with ethyl acetate. The organic extract was washed with
brine, dried over sodium sulfate, and evaporated in vacuo to
afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetic acid 1,1-dioxide (44 mg) as a colorless
powder.

35 mp: 191-193°C

IR (KBr): 1711, 1290, 1244, 1124 cm^{-1}

NMR (CDCl_3 , δ): 1.75-2.05 (2H, m), 2.15 (2H, m), 2.6-2.85 (2H, m), 3.08-3.15 (2H, m), 3.21 (1H, d, $J=15.6\text{Hz}$), 3.60 (1H, d, $J=15.6\text{Hz}$), 6.94-7.01 (4H, m), 7.31 (2H, dd, $J=6.7, 2.1\text{Hz}$), 7.59 (2H, d, $J=9.0\text{Hz}$)

(-) API-ES MS m/z : 393 (M^+-H)

Anal. Calcd. for $\text{C}_{19}\text{H}_{19}\text{ClO}_5\text{S}$: C 57.79, H 4.85

Found: C 57.88, H 4.83

Example 2

A mixture of ethyl 2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (100 mg) and lithium hydroxide monohydrate (42.8 mg) in a mixture of methanol and water was stirred for 4 hours at 60°C . After cooling to room temperature, the mixture was acidified with 4N hydrochloric acid and concentrated in vacuo. The residue was partitioned between ethyl acetate and 1N hydrochloric acid. The separated organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo to give 2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (93 mg) as a crystalline solid.

NMR ($\text{DMSO}-d_6$, δ): 1.44-1.80 (4H, m), 2.26-2.54 (3H, m), 2.62-2.79 (2H, m), 3.00 (1H, d, $J=14.5\text{Hz}$), 3.75 (3H, s), 6.89 (2H, d, $J=9\text{Hz}$), 7.48 (2H, d, $J=9\text{Hz}$)

MS (ESI-) m/z : 265 ($\text{M}-\text{H}$)

Example 3

To a solution of ethyl 2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (315 mg) in methanol (4 ml) was added 1N sodium hydroxide aqueous solution (1.3 ml) at 0°C and the mixture was stirred for 5 hours at room temperature. The resulting mixture was evaporated to remove methanol. The residue was acidified

with 1N hydrochloric acid (HCl) and extracted with ethyl acetate (x3). The combined organic layer was washed with brine, dried over magnesium sulfate and concentrated to give

5 2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (296 mg) as white solid.

NMR (CDCl₃, δ): 1.58-1.92 (4H, m), 2.20-2.32 (1H, m),
2.57-2.68 (2H, m), 2.70-2.81 (1H, m), 2.89 (1H, d, J=14Hz), 2.97 (1H, d, J=14Hz), 6.97-7.08 (4H, m),
7.48-7.56 (2H, m)

10 MS (ESI-) m/z: 335 (M-H)

Example 4

To a solution of methyl 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide in
15 methanol (MeOH) (5 ml) was added solution of lithium hydroxide monohydrate (375 mg) in water (H₂O) (5 ml) at room temperature. After being stirred at 60°C for 2 hours, the mixture was concentrated in vacuo to remove MeOH. The residual solution was acidified by 1M hydrochloric acid and
20 extracted with ethyl acetate (AcOEt) (20 ml x 2). The combined extract was washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylic acid 1,1-dioxide (320 mg) as an amorphous powder.

25 NMR (CDCl₃, δ): 1.70-1.84 (2H, m), 1.95-2.20 (3H, m),
2.25-2.37 (1H, m), 3.11-3.25 (3H, m), 3.16 (1H, d, J=14Hz), 6.91 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz),
7.11 (1H, t, J=8Hz), 7.20 (2H, d, J=8Hz), 7.33 (2H, t, J=8Hz)

30 MS (ESI-) m/z: 359 (M-H)

Example 5

2-(4-Phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylic acid (280 mg) was obtained in a similar manner to
35 that of Example 4.

NMR (CDCl₃, δ): 1.45-2.02 (5H, m), 2.35-2.46 (1H, m),
2.52-2.65 (1H, m), 2.68-2.85 (1H, m), 3.07 (2H, dd,
J=3, 14Hz), 6.90 (2H, d, J=8Hz), 6.99 (2H, d,
J=8Hz), 7.09 (1H, t, J=8Hz), 7.13 (2H, d, J=8Hz),
7.32 (2H, t, J=8Hz)

MS (ESI-) m/z: 327 (M-H)

Example 6

To a solution of ethyl 2-(4-phenoxyphenyl)-1,3-dithiane-2-acetate (370 mg) in ethanol (4 ml) was added 1N sodium hydroxide aqueous solution (2 ml) and the mixture was stirred at 50°C for 3 hours. The resulting mixture was evaporated to remove ethanol. The residue was acidified with 1N HCl and extracted with diethyl ether. The organic layer was washed with brine, and dried over magnesium sulfate. The solvent was evaporated to give 2-(4-phenoxyphenyl)-1,3-dithiane-2-acetic acid (280 mg) as white crystal.

NMR (CDCl₃, δ): 2.03 (2H, br), 2.83 (4H, br), 3.22 (2H, br), 6.93-7.05 (4H, m), 7.13 (1H, d, J=7.0Hz), 7.41-7.48 (2H, m), 7.82-7.86 (2H, m)

MS (ESI-) m/z: 345.1 (M-H)

Example 7

1.5M Solution of lithium diisopropylamide mono-tetrahydrofuran in cyclohexane (1.60 ml) was added dropwise to a stirred solution of 2-[4-(4-chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene 1,1-dioxide (646 mg) in tetrahydrofuran (6.5 ml) under a nitrogen atmosphere and dry ice - acetone cooling, and the resultant solution was stirred under the same conditions for 35 minutes. A solution of allyl bromide (532 mg) in tetrahydrofuran (1.9 ml) was added dropwise therein and the resultant mixture was stirred under the same conditions for 1 hour and 30 minutes.

After addition of a saturated aqueous solution of ammonium

chloride (10 ml) under the same conditions, the reaction mixture was extracted with ethyl acetate. The extract was washed successively with 1N hydrochloric acid and a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and evaporated in vacuo to afford an oil (0.68 g).

Potassium permanganate (259 mg), sodium periodate (1.75 g), and potassium carbonate (618 mg) was successively added to a stirred emulsion of the obtained oil in tert-butyl alcohol (22 ml) and water (38 ml) at room temperature and the resulting mixture was stirred at the same temperature for 1 hour and 40 minutes. The reaction mixture was acidified to pH c.a. 1.0 with 1N hydrochloric acid (10 ml) under ice cooling, and then sodium bisulfite was added portionwise therein under the same condition till the mixture became yellow. The yellow mixture was extracted with ethyl acetate. The extract was washed with an aqueous solution of sodium bisulfite and brine, dried over sodium sulfate, and evaporated in vacuo. The powdery residue was washed with a mixture of diisopropyl ether - diethyl ether to afford a colorless powder (401 mg), 388 mg of which was chromatographed (eluent: toluene - ethyl acetate - acetic acid) over silica gel to afford an oil. The obtained oil was powdered from n-hexane to afford 2-[4-(4-chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene-2-acetic acid 1,1-dioxide (306 mg) as a colorless amorphous powder.

mp: 45-50°C

IR (KBr): 2750-2400, 1734, 1716, 1300, 1244, 1126 cm^{-1}

NMR (DMSO- d_6 , δ): 2.16-2.25 (2H, m), 2.65-2.77 (2H, m), 3.08-3.41 (4H, m), 7.00-7.10 (4H, m), 7.41-7.51 (4H, m), 12.38 (1H, br)

(-) API-ES MS m/z : 379 and 381 ($M^+ - H$)

Anal. Calcd. for $C_{18}H_{17}ClO_5S$: C 56.76, H 4.50

Found: C 57.32, H 5.04

Example 8

Potassium permanganate (172 mg), sodium periodate (1.28 g), and potassium carbonate (409 mg) was successively added to a stirred emulsion of 2-allyl-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran 1,1-dioxide (372 mg) in tert-butyl alcohol (15 ml) and water (26 ml) at room temperature and the resulting mixture was stirred at the same temperature for 1 hour and 30 minutes. The reaction mixture was acidified to pH c.a. 1.0 with conc. hydrochloric acid under ice cooling, and then sodium bisulfite was added portionwise therein under the same condition till the mixture became yellow. The yellow mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: toluene - ethyl acetate - acetic acid) over silica gel to afford a colorless powder (277 mg), which was washed with n-hexane to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (250 mg) as a colorless powder.

mp: 191-193°C

Example 9

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-6-methyl-2H-thiopyran-2-acetic acid 1,1-dioxide (59 mg) was prepared in a similar manner to that of Example 8.

IR (KBr): 3442, 1735, 1714, 1284, 1245, 1124 cm^{-1}

NMR (DMSO- d_6 , δ): 1.16 (3H, d, $J=6.6\text{Hz}$), 1.62-1.98 (4H, m), 2.47-2.63 (2H, m), 3.2-3.59 (3H, m), 6.98-7.10 (4H, m), 7.46 (2H, d, $J=9.0\text{Hz}$), 7.55 (2H, d, $J=9.0\text{Hz}$)

(-) API-ES MS m/z : 407 and 409 (M^+-H)

Example 10

A suspension of (2R or 2S)-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-N-((1R)-1-phenylethyl)-2H-

thiopyran-2-acetamide 1,1-dioxide (diastereomer A, 149 mg) obtained in Example 31 in a mixture of 14N sulfuric acid (7.0 ml) and 1,4-dioxane (4.2 ml) was stirred under reflux for 21 hours and cooled to room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine (twice), dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: dichloromethane - methanol) over silica gel to afford (2R or 2S)-(-)-2-[4-(4-chlorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (an optical isomer A, 109 mg) as a crude brown gum.

IR (KBr): 1734, 1716, 1284, 1244, 1122 cm^{-1}

NMR (CDCl_3 , δ): 1.93 (2H, m), 2.14 (2H, m), 2.6-2.85 (2H, m), 3.08-3.16 (2H, m), 3.22 (1H, d, $J=15.6\text{Hz}$), 3.62 (1H, d, $J=15.6\text{Hz}$), 6.95-7.04 (4H, m), 7.28-7.35 (2H, m), 7.60 (2H, d, $J=9.0\text{Hz}$)

(-) API-ES MS m/z : 393 and 395 (M^+-H)

$[\alpha]_D^{25}$: -32.3° ($C=1.0$, MeOH)

Analytical chiral HPLC:

column: Chiralpak AS (4.6 x 250 mm,

Daicel Chemical Industries, Ltd.)

eluent: n-hexane-ethanol-TFA (700:300:1)

flow rate: 1.0 ml/minute

detection: 220 nm

retention time: 50.0 minutes

Example 11

(2R or 2S)-2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (an optical isomer B, 77 mg) was prepared from (2R or 2S)-(+)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-((1R)-1-phenylethyl)-2H-thiopyran-2-acetamide 1,1-dioxide (diastereomer B, 133 mg) obtained in Example 31 in a similar manner to that of Example 10.

IR (KBr): 1711, 1290, 1242, 1122 cm^{-1}

NMR (CDCl_3 , δ): 1.82-1.95 (2H, m), 2.10-2.15 (2H, m),
2.62-2.80 (2H, m), 3.03-3.11 (2H, m), 3.21 (1H, d,
J=15.6Hz), 3.60 (1H, d, J=15.6Hz), 6.92-7.01 (4H,
m), 7.28-7.34 (2H, m), 7.59 (2H, d, J=9.0Hz)

(-) API-ES MS m/z: 393 ($\text{M}^+ - \text{H}$)

Analytical chiral HPLC:

column: Chiralpak AS (4.6 x 250 mm,
Daicel Chemical Industries, Ltd.)

eluent: n-hexane-ethanol-TFA (700:300:1)

flow rate: 1.0 ml/minute

detection: 220 nm

retention time: 8.96 minutes

Example 12

To a solution of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (16.8 g) in ethyl acetate (420 ml) was added (R)-(+)- α -methylbenzylamine (2.84 g) at room temperature. After being stirred overnight at the same temperature, the resulting crystal was filtrated and washed with ethyl acetate to give (2R or 2S)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (R)-(+)- α -methylbenzylamine salt (9.43 g). A suspension of resulting salt in ethyl acetate (200 ml) was washed with 1N hydrochloric acid (100 ml x 2), water and brine, and concentrated to give the free acid. This procedure was repeated three times (second: amine 0.75 eq; third: 0.85 eq) to give the optically resolved (2R or 2S)-(-)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (an optical isomer A) (4.75 g) as a white solid.

$[\alpha]_D^{25}$: -32.3° (C=1.0, MeOH)

Optical purity: 91% ee

Analytical chiral HPLC:

column: Chiralpak AS (4.6 x 250 mm,
Daicel Chemical Industries, Ltd.)
eluent: n-hexane-ethanol-TFA (700:300:1)
flow rate: 1.0 ml/minutes
detection: 220 nm
retention time: 50.0 minutes

Example 13

To a solution of 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (1 g) in ethanol (8 ml) was added (R)-(+)- α -methylbenzylamine (185 mg) at room temperature. After being stirred overnight at the room temperature, the resulting crystal was filtrated and washed with ethanol to give 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (R)-(+)- α -methylbenzylamine salt. A suspension of resulting salt in ethyl acetate was washed with 1N hydrochloric acid and brine, and concentrated to give the free acid. This procedure was repeated two times to give the optically resolved (2R or 2S)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (300 mg) as a white solid.

NMR (DMSO- d_6 , δ): 1.74-1.87 (4H, m), 2.30-2.37 (1H, m), 3.07-3.56 (5H, m), 7.02 (1H, d, J=4.2Hz), 7.21 (1H, d, J=4.2Hz)

MS (ESI-) m/z: 351 (M-H)

$[\alpha]_D^{25}$: -25.3° (C=1.0, MeOH)

Optical purity: 95% ee

Analytical chiral HPLC:

column: Chiralpak AS (4.6 x 250 mm,
Daicel Chemical Industries, Ltd.)
eluent: n-hexane-ethanol-trifluoroacetic acid
(TFA) (700:300:1)
flow rate: 1.0 ml/minute
detection: 220 nm

retention time: 20.2 minutes

Example 14

A mixture of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (98.7 mg), ammonium formate (78.8 mg), and 10% palladium - carbon (50% wet, 60 mg) in ethanol (5 ml) was stirred under reflux for 3 hours and 20 minutes, and filtered. The filtrate was evaporated in vacuo and the residue was partitioned between ethyl acetate and 0.1N hydrochloric acid. The organic layer was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was powdered from diisopropyl ether to afford 3,4,5,6-tetrahydro-2-(4-phenoxyphenyl)-2H-thiopyran-2-acetic acid 1,1-dioxide (87 mg) as a colorless powder.

mp: 208.5-209.5°C

IR (KBr): 2750-2550, 1707, 1290, 1246, 1124 cm^{-1}

NMR (CDCl_3 , δ): 1.75-2.25 (4H, m), 2.74 (2H, m), 3.11 (2H, m), 3.21 (1H, d, $J=15.6\text{Hz}$), 3.61 (1H, d, $J=15.6\text{Hz}$), 6.97-7.07 (4H, m), 7.14 (1H, t, $J=7.4\text{Hz}$), 7.36 (2H, t, $J=7.7\text{Hz}$), 7.59 (2H, d, $J=9.0\text{Hz}$)

(-) API-ES MS m/z : 359 (M^+-H)

Example 15

A solution of oxalyl chloride (76.2 mg) in dichloromethane (0.7 ml) was added dropwise to a stirred suspension of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (118 mg) and N,N-dimethylformamide (1.10 mg) in dichloromethane (1.2 ml) under ice cooling and a nitrogen atmosphere, then the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours and evaporated in vacuo. The residue was dissolved in dichloromethane (1.6 ml) and the solution was added dropwise to a stirred mixture of

hydroxylammonium chloride (125 mg), 1N aqueous solution of sodium hydroxide (1.8 ml), tetrahydrofuran (3.6 ml), and tert-butyl alcohol (1.8 ml) at room temperature and the resulting mixture was stirred at room temperature for 2 hours and 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: toluene - ethyl acetate - acetic acid) over silica gel (2.6 g) to afford a colorless powder, which was washed with diisopropyl ether to afford 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-hydroxy-2H-thiopyran-2-acetamide 1,1-dioxide (88 mg) as a colorless powder.

mp: 179-180°C (dec.)

IR (KBr): 3421, 3315, 3220, 1652, 1284, 1248, 1119 cm^{-1}

NMR (DMSO- d_6 , δ): 1.74-1.99 (4H, m), 2.5 (1H, m), 2.87 (1H, br d, $J=13.8\text{Hz}$), 3.01-3.55 (4H, m), 6.87-7.12 (4H, m), 7.42-7.59 (4H, m), 8.73 (1H, s), 10.48 (1H, s)

(+) API-ES MS m/z : 432 ($\text{M}^+ + \text{Na}$)

Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{ClNO}_5\text{S}$: C 55.68, H 4.92, N 3.42

Found: C 55.67, H 5.28, N 3.23

Example 16

A solution of oxalyl chloride (55.8 mg) in dichloromethane (0.5 ml) was added dropwise to a stirred solution of crude (2R or 2S)-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (an optical isomer A, 87 mg) obtained in Example 12 and N,N-dimethylformamide (0.80 mg) in dichloromethane (0.88 ml) under ice cooling and a nitrogen atmosphere, then the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 2 hours and 30 minutes, and evaporated in vacuo. The residue was dissolved in

dichloromethane (0.9 ml) and the solution was added dropwise to a stirred mixture of hydroxylammonium chloride (91.7 mg), 1N aqueous solution of sodium hydroxide (1.3 ml), tetrahydrofuran (2.6 ml), and tert-butyl alcohol (1.3 ml) at room temperature and the resulting mixture was stirred at the same temperature for 1 hour and 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: toluene - ethyl acetate - acetic acid) over silica gel (1.9 g) to afford a pale brown powder (67 mg), which was washed with diisopropyl ether to afford (R or S)-(-)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-hydroxy-2H-thiopyran-2-acetamide 1,1-dioxide (optical isomer A, 55 mg) as a colorless powder.

mp: 183.5-187°C (dec.)

$[\alpha]_D^{28}$: -9.3° (C=0.71, MeOH)

IR (KBr): 3446, 3423, 1653, 1284, 1250, 1119 cm⁻¹

NMR (DMSO-d₆, δ): 1.75-2.05 (4H, m), 2.5 (1H, m), 2.87 (1H, br d, J=12.9Hz), 3.01-3.5 (4H, m), 7.00 (2H, d, J=8.9Hz), 7.08 (2H, d, J=8.9Hz), 7.46 (2H, d, J=8.9Hz), 7.56 (2H, d, J=8.9Hz), 8.73 (1H, s), 10.48 (1H, s)

(+) API-ES MS m/z: 432 and 434 (M⁺+Na)

(-) API-ES MS m/z: 408 and 410 (M⁺-H)

Analytical chiral HPLC:

column: Chiralpak AS (4.6 x 250 mm,

Daicel Chemical Industries, Ltd.)

eluent: n-hexane-ethanol-TFA (700:300:1)

flow rate: 1.0 ml/minute

detection: 220 nm

retention time: 18.2 minutes

Example 17

(R or S)-(+)-2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-

tetrahydro-N-hydroxy-2H-thiopyran-2-acetamide 1,1-dioxide (41 mg) was prepared from crude (2R or 2S)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (an optical isomer B, 87 mg) obtained in Example 11 in a similar manner to that of Example 16.

mp: 187-188°C (dec.)

$[\alpha]_D^{28}$: 10.5° (C=0.56, MeOH)

IR (KBr): 3444, 3423, 3317, 3224, 1655, 1284, 1250, 1122 cm⁻¹

NMR (DMSO-d₆, δ): 1.75-2.05 (4H, m), 2.5 (1H, m), 2.87 (1H, br d, J=13.6Hz), 3.01-3.52 (4H, m), 7.00 (2H, d, J=8.9Hz), 7.08 (2H, d, J=8.9Hz), 7.46 (2H, d, J=8.9Hz), 7.56 (2H, d, J=8.9Hz), 8.73 (1H, s), 10.48 (1H, s)

(+) API-ES MS m/z: 432 and 434 (M⁺+Na)

(-) API-ES MS m/z: 408 and 410 (M⁺-H)

Analytical chiral HPLC:

column: Chiralpak AS (4.6 x 250 mm,

Daicel Chemical Industries, Ltd.)

eluent: n-hexane-ethanol-TFA (700:300:1)

flow rate: 1.0 ml/minute

detection: 220 nm

retention time: 27.9 minutes

Example 18

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-N-hydroxy-6-methyl-2H-thiopyran-2-acetamide 1,1-dioxide (30 mg) was prepared from 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-6-methyl-2H-thiopyran-2-acetic acid 1,1-dioxide (55 mg) in a similar manner to that of Example 15.

mp: 102°C (dec.)

IR (KBr): 3446 and 3421 (br), 1668, 1282, 1246, 1124 cm⁻¹

NMR (DMSO-d₆, δ): 1.17 (3H, d, J=6.6Hz), 1.5-2.05 (4H,

m), 2.4 (1H, m), 2.8-2.95 (1H, br d), 3.09 (1H, d, J=15.0Hz), 3.23 (1H, d, J=15.0Hz), 3.54 (1H, m), 7.00 (2H, d, J=8.8Hz), 7.08 (2H, d, J=8.9Hz), 7.42-7.49 (2H, m), 7.56 (2H, d, J=8.9Hz), 8.73 (1H, s), 10.49 (1H, s)

(+) API-ES MS m/z: 446 and 448 (M^+ +Na)

Example 19

3,4,5,6-Tetrahydro-N-hydroxy-2-(4-phenoxyphenyl)-2H-thiopyran-2-acetamide 1,1-dioxide (41 mg) was prepared from 3,4,5,6-tetrahydro-2-(4-phenoxyphenyl)-2H-thiopyran-2-acetic acid 1,1-dioxide (66 mg) in a similar manner to that of Example 15.

mp: 182-183°C (dec.)

IR (KBr): 3446 and 3423 (br), 1655, 1288, 1246, 1115 cm^{-1}

NMR (DMSO- d_6 , δ): 1.75-2.05 (4H, m), 2.4 (1H, m), 2.87 (1H, br d, J=13.0Hz), 3.04-3.55 (4H, m), 6.96 (2H, d, J=8.9Hz), 7.06 (2H, d, J=7.5Hz), 7.19 (1H, t, J=7.3Hz), 7.43 (2H, t, J=7.4Hz), 7.54 (2H, d, J=8.9Hz), 8.74 (1H, s), 10.48 (1H, s)

(+) APCI MS m/z: 376 (M^+ +H), 343 (M^+ -NHOH)

(-) API-ES MS m/z: 374 (M^+ -H)

Example 20

2-[4-(4-Chlorophenoxy)phenyl]-2,3,4,5-tetrahydro-N-hydroxy-2-thiophene-2-acetamide 1,1-dioxide (88 mg) was prepared from 2-[4-(4-chlorophenoxy)phenyl]-2,3,4,5-tetrahydrothiophene-2-acetic acid 1,1-dioxide (122 mg) in a similar manner to that of Example 15.

mp: 63-68°C (dec.)

IR (KBr): 3423 (br), 1662, 1296, 1244, 1126 cm^{-1}

NMR (DMSO- d_6 , δ): 2.19-2.23 (2H, m), 2.56-3.28 (6H, m), 6.99-7.10 (4H, m), 7.38-7.48 (4H, m), 8.73 (1H, s), 10.40 (1H, s)

(+) APCI MS m/z: 396 and 398 ($M^+ + H$),
363 and 365 ($M^+ - NHOH$)

Anal. Calcd. for $C_{18}H_{18}ClNO_5S$: C 54.61, H 4.58, N 3.54

Found: C 55.20, H 5.06, N 3.26

5

Example 21

To a solution of potassium hydroxide (400 g) in water (200 ml) was added a solution of ethyl 7-amidinothio-3-[4-(4-chlorophenoxy)phenyl]hept-2-enoate hydroiodide (70.1 g) in tetrahydrofuran (100 ml), and the mixture was refluxed overnight. After the solution was cooled and acidified with 1N HCl, the mixture was extracted with ethyl acetate (100 ml x 3). The combined organic layer was washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure to give 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (60 g) as a yellow oil.

NMR ($CDCl_3$, δ): 1.51-1.90 (4H, m), 2.26-2.38 (1H, m), 2.48-2.68 (3H, m), 2.90 (2H, d, $J=14$ Hz), 2.98 (2H, d, $J=14$ Hz), 6.94 (4H, d, $J=8$ Hz), 7.27 (2H, d, $J=8$ Hz), 7.57 (2H, d, $J=8$ Hz)

MS (ES-) m/z: 361 (M-H)

Example 22

2-[4-(4-Bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (3.99 g) was obtained in a similar manner to that of Example 21.

NMR ($CDCl_3$, δ): 1.50-1.87 (4H, m), 2.27-2.49 (1H, m), 2.47-2.70 (3H, m), 2.90 (1H, d, $J=15$ Hz), 3.00 (1H, d, $J=15$ Hz), 6.96 (4H, d, $J=9$ Hz), 7.44 (4H, d, $J=9$ Hz)

MS (ESI-) m/z: 407 (M-H)

Example 23

Ethyl 2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-

tetrahydro-2H-thiopyran-2-acetate (117 mg) was obtained from 7-amidinothio-3-[5-(4-fluorophenyl)-2-thienyl]hept-2-enoate hydroiodide in a similar manner to that of Example 21.

5 NMR (CDCl₃, δ): 1.12 (3H, t, J=7Hz), 1.49-1.92 (4H, m), 2.18-2.30 (1H, m), 2.55-2.68 (2H, m), 2.73-2.82 (1H, m), 2.81 (1H, d, J=14Hz), 2.89 (1H, d, J=14Hz), 4.01 (2H, q, J=7Hz), 6.93-7.11 (4H, m), 7.49-7.56 (2H, m)

10 Example 24

To a solution of ethyl 3-(4-biphenyl)-7-chlorohept-2-enoate (0.90 g) in acetone (15 ml) was added NaI (1.55 g) at 60°C. After being stirred overnight, the reaction mixture was cooled, concentrated in vacuo, diluted with water, and
15 extracted with ether. The ether extract was washed with brine, dried over MgSO₄ and concentrated in vacuo. A mixture of this residue and thiourea (158 mg) in ethanol (EtOH) (15 ml) was refluxed with stirring for 24 hours. The resulting mixture was cooled and concentrated in vacuo to
20 yield the isothiuronium salt. To a solution of potassium hydroxide (KOH) (1.74 g) in water was added this isothiuronium salt, and the mixture was refluxed with stirring for 8 hours. The reaction mixture was cooled at 0°C and was quenched by cautious dropwise addition of a solution
25 of 50% aqueous sulfuric acid (H₂SO₄) until acidic. The mixture was extracted with ether, and the organic layers were washed with water and brine, dried over magnesium sulfate (MgSO₄) and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: 5%
30 methanol (MeOH) in chloroform (CHCl₃) to give 2-(4-biphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (335 mg) as an amorphous.

35 NMR (CDCl₃, δ): 1.60-1.85 (4H, m), 2.30-2.39 (1H, m), 2.50-2.70 (3H, m), 2.94 (1H, d, J=14.7Hz), 3.01 (1H, d, J=14.7Hz), 7.34 (1H, dd, J=7, 7Hz), 7.56-

7.61 (4H, m), 7.68-7.71 (2H, m)
MS (ESI-) m/z: 311 (M-H)

Example 25

5 2-[4-(4-Fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetic acid (200 mg) was obtained in a similar
manner to that of Example 24.

NMR (CDCl₃, δ): 1.60-1.84 (4H, m), 2.27-2.36 (1H, m),
2.50-2.67 (3H, m), 2.88 (1H, d, J=15Hz), 2.97 (1H,
10 d, J=16Hz), 6.91 (2H, d, J=9Hz), 6.99-7.06 (4H, m),
7.56 (2H, d, J=9Hz)
MS (ESI-) m/z: 345 (M-H)

Example 26

15 2-[4-(4-Chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetic acid (310 mg) was obtained in a similar
manner to that of Example 24.

NMR (CDCl₃, δ): 1.60-1.85 (4H, m), 2.29-2.38 (1H, m),
2.52-2.69 (3H, m), 2.94 (1H, d, J=14.7Hz), 3.01
20 (1H, d, J=14.7Hz), 7.39 (2H, d, J=8Hz), 7.50-7.54
(4H, m), 7.69 (2H, d, J=8Hz)
MS (ESI-) m/z: 345 (M-H)

Example 27

25 2-[4-(4-Bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetic acid (120 mg) was obtained in a similar
manner to that of Example 24.

NMR (CDCl₃, δ): 1.61-1.85 (4H, m), 2.29-2.36 (1H, m),
2.51-2.69 (3H, m), 2.94 (1H, d, J=14.7Hz), 3.01
30 (1H, d, J=14.7Hz), 7.45 (2H, d, J=9Hz), 7.51-7.57
(4H, m), 7.69 (2H, d, J=9Hz)
MS (ESI-) m/z: 389 (M-H)

Example 28

35 2-[4-(4-Fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-

thiopyran-2-acetic acid (200 mg) was obtained in a similar manner to that of Example 24.

5 NMR (CDCl₃, δ): 1.60-1.85 (4H, m), 2.29-2.38 (1H, m),
2.53-2.67 (2H, m), 2.94 (1H, d, J=15Hz), 3.01 (1H,
d, J=16Hz), 7.07-7.12 (2H, m), 7.51-7.56 (4H, m),
7.69 (2H, d, J=8.5Hz)
MS (ESI-) m/z: 329 (M-H)

Example 29

10 2-[5-(4-Chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (2.5 g) was obtained in a similar manner to that of Example 24.

15 NMR (DMSO-d₆, δ): 1.55-1.75 (4H, m), 2.25-2.32 (1H, m), 2.45-2.63 (3H, m), 2.74 (1H, d, J=14Hz), 3.97 (1H, d, J=14Hz), 7.02 (1H, d, J=3.6Hz), 7.40 (1H, d, J=3.6Hz), 7.45 (2H, d, J=8.7Hz), 7.64 (2H, d, J=8.7Hz)

MS (ESI-) m/z: 351 (M-H)

20 Example 30

2-(5-Bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (8.5 g) was obtained in a similar manner to that of Example 24.

25 NMR (DMSO-d₆, δ): 1.45-1.73 (4H, m), 2.12-2.20 (1H, m), 2.45-2.70 (4H, m), 2.87 (1H, d, J=14.4Hz), 6.84 (1H, d, J=4.2Hz), 7.08 (1H, d, J=4.2Hz)

Example 31

30 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCD) hydrochloride (205 mg) was added to a stirred mixture of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (326 mg), (R)-(+)- α -methylbenzylamine (105 mg), and 1-hydroxybenzotriazole (123 mg) in dichloromethane (8 ml) under ice cooling, and then the
35 resulting mixture was stirred at the same temperature for 2

hours and at room temperature for 2 hours and extracted with dichloromethane. The extract was washed successively with water, 0.1N hydrochloric acid, water, and a saturated aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (eluent: toluene - ethyl acetate) over silica gel to afford diastereomer A (180 mg) and diastereomer B (181 mg) of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-N-[(1R)-1-phenylethyl]acetamide 1,1-dioxide as a colorless solid and colorless crystals, respectively.

Diastereomer A:

mp: 138-160.5°C

$[\alpha]_D^{27}$: 31.0° (C=0.52, MeOH)

IR (KBr): 3421 (br), 1651, 1288, 1244, 1124 cm⁻¹

NMR (CDCl₃, δ): 1.06 (3H, d, J=6.8Hz), 1.94-2.15 (4H, m), 2.68-2.74 (2H, m), 2.99-3.26 (4H, m), 4.72-4.87 (1H, m), 5.21 (1H, br d, J=8.0Hz), 6.97 (2H, d, J=9.0Hz), 7.00-7.11 (4H, m), 7.19-7.37 (5H, m), 7.70 (2H, d, J=9.0Hz)

(+) APCI MS m/z: 498 and 500 (M⁺+H)

Diastereomer B:

mp: 82.5-89°C

$[\alpha]_D^{27}$: 53.4° (C=0.50, MeOH)

IR (KBr): 3365 (br), 1651, 1288, 1246, 1122 cm⁻¹

NMR (CDCl₃, δ): 1.32 (3H, d, J=6.9Hz), 1.91 (2H, m), 2.13 (2H, m), 2.62 (2H, m), 2.99-3.30 (4H, m), 4.85 (1H, m), 5.31 (1H, br d, J=8.0Hz), 6.74-6.80 (2H, m), 6.90-6.99 (4H, m), 7.15-7.36 (5H, m), 7.58 (2H, d, J=9.0Hz)

(+) APCI MS m/z: 498 and 500 (M⁺+H)

Example 32

To a solution of (2R or 2S)-2-[4-(4-chlorophenoxy)-

phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid
1,1-dioxide (4.75 g) obtained in Example 10, O-(2-
tetrahydropyranyl)hydroxylamine (2.11 g), and
1-hydroxybenzotriazole (1.95 g) in N,N-dimethylformamide (60
5 ml) was added WSCD hydrochloride (2.77 g). After being
stirred for 4 hours at room temperature, the solvent was
evaporated in vacuo, and the resulting residue was dissolved
in ethyl acetate (60 ml). The solution was washed with 5%
aqueous citric acid solution, saturated sodium bicarbonate
10 solution and brine, and dried over magnesium sulfate. The
solution was concentrated under reduced pressure to give (2R
or 2S)-N-(2-tetrahydropyranyloxy)-2-[4-(4-chlorophenoxy)-
phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (6.52 g) as a slightly yellow oil.

15 NMR (CDCl₃, δ): 1.46-2.22 (10H, m), 2.77 (1H, br),
3.02-3.28 (4H, m), 3.38-3.55 (1H, m), 3.65-3.78
(1H, m), 4.37 (0.5H, s), 4.77 (0.5H, s), 6.95 (2H,
d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.29 (2H, d,
J=8Hz), 7.65 (2H, d, J=8Hz), 8.28 (1H, br)
20 MS (ESI-) m/z: 493 (M-H)

The following compounds were obtained in a similar
manner to that of Example 32.

25 Example 33

2-[4-(4-Chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide (140 mg)

NMR (CDCl₃, δ): 1.42-1.91 (10H, m), 2.23-2.36 (1H,
m), 2.49-2.72 (4H, m), 2.74-2.83 (1H, m), 3.45-
30 3.58 (1H, m), 3.71-3.83 (1H, m), 4.55 (1H, s),
4.79 (0.5H, s), 6.89-7.03 (4H, m), 7.27 (2H, d,
J=8Hz), 7.60 (2H, d, J=8Hz), 7.96 (0.5H, s), 8.16
(0.5H, s)

MS (ESI-) m/z: 460 (M-H)

Example 34

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (307 mg)

5 NMR (CDCl₃, δ): 1.53-1.70 (10H, m), 2.08-2.17 (2H, m),
2.73-2.76 (2H, m), 3.02-3.23 (4H, m), 3.42-3.52
(1H, m), 6.98-7.05 (6H, m), 7.64 (2H, d, J=9Hz)
MS (ESI-) m/z: 476 (M-H)

10 Example 35

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (250 mg)

15 NMR (CDCl₃, δ): 1.50-1.64 (6H, m), 1.74-1.78 (4H, m),
2.25-2.34 (2H, m), 2.52-2.70 (4H, m), 2.76-2.82
(1H, m), 3.49-3.57 (1H, m), 3.72-3.83 (1H, m),
6.95-7.04 (6H, m), 7.59 (2H, d, J=9Hz)
MS (ESI-) m/z: 444 (M-H)

Example 36

20 N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1-oxide
(152 mg)

25 NMR (CDCl₃, δ): 1.54-1.81 (10H, m), 2.45-2.56 (2H, m),
2.75-2.96 (5H, m), 3.53-3.59 (1H, m), 3.81-3.87
(1H, m), 6.95-7.04 (6H, m), 7.39 (2H, d, J=9Hz)
MS (ESI-) m/z: 460 (M-H)

Example 37

30 N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenoxy)-phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (173 mg)

35 NMR (CDCl₃, δ): 1.45-1.75 (6H, m), 1.89-2.01 (2H, m),
2.06-2.20 (2H, m), 2.68-2.80 (2H, m), 3.00-3.24
(4H, m), 3.40-3.55 (1H, m), 3.64-3.75 (1H, m),
4.49 (0.5H, br s), 4.75 (0.5H, br s), 6.93 (2H, d,

J=9Hz), 7.04 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz),
7.67 (2H, d, J=9Hz), 7.77 (2H, d, J=9Hz), 7.77
(0.5H, br s), 7.90 (0.5H, br s)

MS (ESI-) m/z: 536 (M-H)

5

Example 38

N-(2-Tetrahydropyranyloxy)-2-[4-[4-(4-fluorophenyl)-
phenoxy]phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide
1,1-dioxide (122 mg)

10 NMR (CDCl₃, δ): 1.45-1.79 (6H, m), 1.88-2.02 (2H, m),
2.06-2.24 (2H, m), 2.66-2.82 (2H, m), 3.00-3.25
(4H, m), 3.40-3.56 (1H, m), 3.64-3.77 (1H, m),
4.41 (0.5H, br s), 4.75 (0.5H, br s), 7.00-7.18
(6H, m), 7.42-7.56 (4H, m), 7.67 (2H, d, J=9Hz),
15 7.75 (0.5H, br s), 7.89 (0.5H, br s)

MS (ESI-) m/z: 552 (M-H)

Example 39

N-(2-Tetrahydropyranyloxy)-2-(4-methoxyphenyl)-3,4,5,6-
20 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (113 mg)

NMR (CDCl₃, δ): 1.41-1.72 (6H, m), 1.87-2.01 (2H, m),
2.06-2.21 (2H, m), 2.59-2.81 (2H, m), 3.00-3.25
(4H, m), 3.32-3.73 (2H, m), 3.81 (3H, s), 4.37-
4.44 (0.5H, m), 4.69-4.79 (0.5H, m), 6.91-7.03 (2H,
25 m), 7.53-7.69 (2H, m), 7.70-7.91 (1H, m)

MS (ESI-) m/z: 396 (M-H)

Example 40

N-(2-Tetrahydropyranyloxy)-2-[5-(4-fluorophenyl)-2-
30 thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (145
mg)

NMR (CDCl₃, δ): 1.45-1.99 (10H, m), 2.17-2.32 (1H, m),
2.50-2.97 (3H, m), 3.40-3.51 (1H, m), 3.71-3.86
(1H, m), 4.70 (0.5H, s), 4.86 (0.5H, s), 6.93-7.19
35 (4H, m), 7.52-7.67 (2H, m), 8.09 (0.5H, s), 8.22

(0.5H, s)

MS (ESI-) m/z: 434 (M-H)

Example 41

N-(2-Tetrahydropyranyloxy)-2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (345 mg)

NMR (CDCl₃, δ): 1.39-1.79 (6H, m), 1.89-2.00 (2H, m), 2.05-2.27 (2H, m), 2.64-2.92 (2H, m), 3.06 (1H, s), 3.09-3.16 (1H, m), 3.27-3.50 (1H, m), 3.61-3.73 (1H, m), 4.53 (0.5H, br s), 4.82 (1H, br s), 7.02-7.11 (2H, m), 7.16-7.27 (2H, m), 7.55 (1H, d, J=8Hz), 7.57 (1H, d, J=8Hz), 7.97 (0.5H, s), 8.13 (1H, br s)

Example 42

N-(2-Tetrahydropyranyloxy)-2-(4-biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (330 mg)

NMR (CDCl₃, δ): 1.45-1.81 (10H, m), 2.29-2.38 (1H, m), 2.52-2.96 (7H, m), 3.58-3.75 (1H, m), 7.35-7.37 (1H, m), 7.42-7.47 (2H, m), 7.56-7.64 (4H, m), 7.71-7.75 (2H, m)

MS (ESI-) m/z: 410 (M-H)

Example 43

N-(2-Tetrahydropyranyloxy)-2-(4-biphenylyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (390 mg)

NMR (CDCl₃, δ): 1.38-1.66 (6H, m), 1.95-2.03 (2H, m), 2.12-2.21 (2H, m), 2.73-2.84 (2H, m), 2.89 (1H, s), 2.96 (1H, s), 3.04-3.31 (4H, m), 3.50-3.62 (1H, m), 7.35-7.47 (3H, m), 7.58-7.60 (2H, m), 7.65-7.70 (2H, m), 7.77-7.81 (2H, m)

MS (ESI-) m/z: 442 (M-H)

Example 44

N-(2-Tetrahydropyranyloxy)-2-[4-(4-chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (300 mg)

5 NMR (CDCl₃, δ): 1.60-1.66 (6H, m), 1.94-2.03 (2H, m),
2.13-2.21 (2H, m), 2.76-2.84 (2H, m), 2.89-2.96
(2H, m), 3.07-3.27 (4H, m), 3.53-3.65 (1H, m),
7.41 (2H, d, J=8.5Hz), 7.51 (2H, d, J=8.5Hz),
7.60-7.64 (2H, m), 7.76-7.80 (2H, m)

MS (ESI-) m/z: 476 (M-H)

10

Example 45

N-(2-Tetrahydropyranyloxy)-2-[4-(4-bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

15 NMR (CDCl₃, δ): 1.44-1.62 (10H, m), 2.10-2.20 (2H, m),
2.76-2.84 (2H, m), 3.05-3.31 (4H, m), 3.53-3.65
(1H, m), 7.45 (2H, d, J=9Hz), 7.56-7.64 (4H, m),
7.70-7.77 (2H, m)

MS (ESI-) m/z: 520 (M-H)

20

Example 46

N-(2-Tetrahydropyranyloxy)-2-[4-(4-fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

25 NMR (CDCl₃, δ): 1.45-1.70 (10H, m), 2.12-2.19 (2H, m),
2.79-2.81 (2H, m), 3.05-3.32 (4H, m), 3.55-3.64
(1H, m), 7.13 (2H, dd, J=9, 9Hz), 7.52-7.61 (4H,
m), 7.73-7.78 (2H, m)

MS (ESI-) m/z: 460 (M-H)

30

Example 47

N-(2-Tetrahydropyranyloxy)-2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide (360 mg)

35 NMR (CDCl₃, δ): 1.45-2.31 (12H, m), 2.42-2.63 (1H, m),
3.03-3.20 (3H, m), 3.43 (1H, d, J=14Hz), 3.57-3.70

(1H, m), 3.84-4.02 (1H, m), 4.91, 5.11 (1H, s),
6.91 (2H, d, J=8Hz), 6.97-7.14 (3H, m), 7.19 (2H,
t, J=8Hz), 7.28-7.48 (2H, m), 9.99, 10.07 (1H, s)
MS (ESI-) m/z: 458 (M-H)

5

Example 48

N-(2-Tetrahydropyranyloxy)-2-(4-phenoxybenzyl)-3,4,5,6-
tetrahydro-2H-thiopyran-2-carboxamide (320 mg)

10 NMR (CDCl₃, δ): 1.33-2.00 (12H, m), 2.47-2.59 (1H, m),
2.64-2.90 (3H, m), 3.08-3.22 (1H, m), 3.50-3.65
(1H, m), 3.75-4.00 (1H, m), 4.70, 4.98 (1H, s),
6.87-7.20 (7H, m), 7.32 (2H, t, J=8Hz), 9.70 (1H,
s)

MS (ESI-) m/z: 426 (M-H)

15

Example 49

N-(2-Tetrahydropyranyloxy)-2-(4-biphenylmethyl)-
3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide
(152 mg)

20 NMR (CDCl₃, δ): 1.54-2.35 (12H, m), 2.45-2.66 (1H, m),
3.08-3.25 (3H, m), 3.33-3.55 (1H, m), 3.56-3.70
(1H, m), 3.82-4.08 (1H, m), 4.95, 5.14 (1H, s),
7.23-7.36 (3H, m), 7.42 (2H, t, J=8Hz), 7.47-7.67
(4H, m), 10.01, 10.08 (1H, s)

25 MS (ESI-) m/z: 442 (M-H)

Example 50

N-(2-Tetrahydropyranyloxy)-2-(4-phenoxyphenyl)-1,3-
dithiane-2-acetamide (150 mg)

30 NMR (DMSO-d₆, δ): 1.47-1.62 (6H, m), 1.85-1.90 (2H,
m), 2.73 (2H, s), 2.89 (4H, br), 3.33 (2H, m),
4.57 (1H, s), 6.98 (2H, d, J=8.0Hz), 7.03 (2H, d,
J=8.0Hz), 7.16 (1H, dd, J=8.0, 8.0Hz), 7.40 (2H,
dd, J=8.0, 8.0Hz), 7.83 (2H, d, J=8.0Hz)

35 MS (ESI-) m/z: 444.1 (M-H)

Example 51

5 N-(2-Tetrahydropyranyloxy)-2-[5-(4-chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (250 mg)

NMR (CDCl₃, δ): 1.45-1.67 (10H, m), 1.90-1.97 (2H, m), 2.67-3.12 (6H, m), 3.62-3.68 (1H, m), 7.24-7.26 (2H, m), 7.35 (2H, d, J=8.7Hz), 7.52 (2H, d, J=8.7Hz)

MS (ESI-) m/z: 482 (M-H)

Example 52

N-(2-Tetrahydropyranyloxy)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (190 mg)

15 NMR (CDCl₃, δ): 1.50-2.17 (11H, m), 2.65-3.10 (6H, m), 3.47-3.58 (1H, m), 3.72-3.81 (1H, m), 7.00-7.05 (2H, m)

MS (ESI-) m/z: 450 (M-H)

Example 53

20 (2R or 2S)-N-(2-Tetrahydropyranyloxy)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80 mg) from (2R or 2S) 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (63 mg) obtained in Example 13

25 NMR (CDCl₃, δ): 1.50-2.17 (11H, m), 2.65-3.10 (6H, m), 3.47-3.58 (1H, m), 3.72-3.81 (1H, m), 7.00-7.05 (2H, m)

MS (ESI-) m/z: 450 (M-H)

Example 54

30 To a mixture of (2R or 2S)-N-(2-tetrahydropyranyloxy)-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (6.51 g) obtained in
35 Example 32 in methanol (40 ml) was added 10% hydrogen

chloride in methanol (10 ml) at room temperature. After being stirred for 30 minutes, the solution was concentrated.

The residue was purified with silica gel column chromatography (eluent: hexane-EtOAc 1:1) to give (2R or 2S)-(-)-N-hydroxy-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (optical isomer A, 4.72 g) as white crystalline.

$[\alpha]_D^{25}$: -13.7°C (C=0.98, MeOH)

Analytical chiral HPLC:

column: Chiralpak AS (4.6 x 250 mm,
Daicel Chemical Industries, Ltd.)
eluent: n-hexane-ethanol-TFA (700:300:1)
flow rate: 1.0 ml/minute
detection: 220 nm
retention time: 18.2 minutes

The following compounds were obtained in a similar manner to that of Example 54.

Example 55

N-Hydroxy-2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (61 mg)

NMR (DMSO- d_6 , δ): 1.32-1.78 (4H, m), 2.30-2.58 (4H, m), 2.60-2.73 (2H, m), 6.96-7.08 (4H, m), 7.43 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 10.19 (1H, s)

MS (ESI-) m/z: 376 (M-H)

Example 56

N-Hydroxy-2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg)

NMR (DMSO- d_6 , δ): 1.75-2.03 (4H, m), 2.99 (1H, d, J=14Hz), 3.19 (1H, d, J=14Hz), 3.34-3.50 (4H, m), 6.94 (2H, d, J=9Hz), 7.09-7.14 (2H, m), 7.23-7.29 (2H, m), 7.53 (2H, d, J=9Hz), 8.74 (1H, s)

MS (ESI-) m/z: 392 (M-H)

Example 57

N-Hydroxy-2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (143 mg)

5 NMR (DMSO-d₆, δ): 1.46-1.73 (4H, m), 2.35-2.49 (4H, m), 2.64-2.71 (2H, m), 6.93 (2H, d, J=9Hz), 7.05-7.09 (2H, m), 7.20-7.26 (2H, m), 7.53 (2H, d, J=9Hz), 8.62 (1H, s), 10.18 (1H, s)

MS (ESI-) m/z: 360 (M-H)

10

Example 58

N-Hydroxy-2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1-oxide (80 mg)

15 NMR (DMSO-d₆, δ): 1.47-1.65 (4H, m), 1.95-2.02 (1H, m), 2.25-2.44 (3H, m), 2.57 (1H, d, J=14Hz), 2.70 (1H, d, J=14Hz), 6.96 (2H, d, J=9Hz), 7.07-7.12 (2H, m), 7.22-7.28 (2H, m), 7.40 (2H, d, J=9Hz), 8.64 (1H, s), 10.31 (1H, s)

MS (ESI-) m/z: 376 (M-H)

20

Example 59

N-Hydroxy-2-[4-(4-bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (104 mg)

25 NMR (CDCl₃, δ): 1.86-1.97 (2H, m), 2.02-2.23 (2H, m), 2.60-2.80 (2H, m), 3.01-3.24 (4H, m), 6.93 (2H, d, J=9Hz), 7.01 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.64 (2H, d, J=9Hz)

MS (ESI-) m/z: 452 (M-H)

30 Example 60

N-Hydroxy-2-[4-[4[(4-fluorophenyl)phenoxy]phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (63 mg)

35 NMR (CDCl₃, δ): 1.87-2.00 (2H, m), 2.04-2.25 (2H, m), 2.60-2.82 (2H, m), 3.01-3.25 (4H, m), 7.00-7.19

(6H, m), 7.47-7.57 (4H, m), 7.64 (2H, d, J=9Hz)
MS (ESI-) m/z: 468 (M-H)

Example 61

5 N-Hydroxy-2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (21 mg)

NMR (DMSO-d₆, δ): 1.70-2.05 (4H, m), 2.39-2.52 (1H, m), 2.81-2.91 (1H, m), 2.95-3.22 (4H, m), 3.26 (3H, s), 6.91 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz), 8.70 (1H, s), 10.46 (1H, s)
10 MS (ESI-) m/z: 312 (M-H)

Example 62

15 N-Hydroxy-2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (87 mg)

NMR (CDCl₃, δ): 1.45-1.85 (4H, m), 2.35-2.74 (4H, m), 2.46 (1H, d, J=14Hz), 2.66 (1H, d, J=14Hz), 7.17-7.33 (3H, m), 7.45 (1H, d, J=3Hz), 7.64-7.77 (2H, m), 8.74 (1H, s)
20 MS (ESI-) m/z: 350 (M-H)

Example 63

N-Hydroxy-2-[5-(4-fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (286 mg)
25 NMR (CDCl₃, δ): 1.69-2.07 (4H, m), 2.35-2.48 (2H, m), 2.94-3.54 (4H, m), 7.17-7.33 (3H, m), 7.45 (1H, d, J=3Hz), 7.64-7.77 (2H, m), 8.74 (1H, s)
MS (ESI-) m/z: 382 (M-H)

30 Example 64

N-Hydroxy-2-(4-biphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide (230 mg)

NMR (DMSO-d₆, δ): 1.61-1.79 (4H, m), 2.39-2.56 (2H, m), 2.65-2.75 (3H, m), 2.89 (1H, s), 7.36 (1H, dd, J=7, 7Hz), 7.47 (2H, dd, J=7, 7Hz), 7.64-7.69 (6H,
35

m), 8.63 (1H, s)

MS (ESI-) m/z: 326 (M-H)

Example 65

5 N-Hydroxy-2-(4-biphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

NMR (DMSO-d₆, δ): 1.77-2.05 (4H, m), 2.49-2.51 (2H, m), 3.19-3.41 (4H, m), 7.41 (1H, dd, J=7.5, 7.5Hz), 7.49 (2H, dd, J=7.5, 7.5Hz), 7.65-7.71 (6H, m), 8.74 (1H, s)

10 MS (ESI-) m/z: 358 (M-H)

Example 66

15 N-Hydroxy-2-[4-(4-chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

NMR (DMSO-d₆, δ): 1.78-2.04 (4H, m), 2.91-3.10 (2H, m), 3.17-3.36 (4H, m), 7.54 (2H, d, J=9Hz), 7.61-7.69 (4H, m), 7.73 (2H, d, J=9Hz), 8.72 (1H, s)

Example 67

20 N-Hydroxy-2-[4-(4-bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

NMR (DMSO-d₆, δ): 1.77-2.06 (4H, m), 2.93-3.08 (2H, m), 3.19-3.36 (4H, m), 7.61-7.70 (8H, m), 8.74 (1H, s)

25 MS (ESI-) m/z: 436 (M-H)

Example 68

30 N-Hydroxy-2-[4-(4-fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

NMR (DMSO-d₆, δ): 1.77-2.05 (4H, m), 2.93-3.54 (6H, m), 7.31 (2H, dd, J=9, 9Hz), 7.63-7.77 (6H, m), 8.73 (1H, s), 10.53 (1H, s)

35 MS (ESI-) m/z: 376 (M-H)

Example 69

N-Hydroxy-2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide (199 mg)

5 NMR (CDCl₃, δ): 1.47-2.20 (5H, m), 2.46-2.62 (1H, m),
2.96-3.20 (3H, m), 3.43 (1H, d, J=14Hz), 6.89 (2H,
d, J=8Hz), 6.98 (2H, d, J=8Hz), 7.05-7.18 (3H, m),
7.33 (2H, d, J=8Hz), 7.96 (1H, br s), 9.98 (1H, br
s)

MS (ESI-) m/z: 374 (M-H)

10

Example 70

N-Hydroxy-2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide (203 mg)

mp: 124-126°C

15 NMR (CDCl₃, δ): 1.22-1.38 (1H, m), 1.45-1.66 (2H, m),
1.70-1.83 (1H, m), 1.88-1.98 (1H, m), 2.43-2.55
(1H, m), 2.60-2.75 (2H, m), 2.80 (1H, d, J=14Hz),
3.15 (1H, d, J=14Hz), 6.90 (2H, d, J=8Hz), 7.00
(2H, d, J=8Hz), 7.05-7.15 (3H, m), 7.33 (2H, t,
20 J=8Hz), 9.47 (1H, s)

MS (ESI-) m/z: 342 (M-H)

Example 71

25 N-Hydroxy-2-(4-biphenylmethyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide (78 mg)

mp: 101-104°C

30 NMR (DMSO-d₆, δ): 1.58-2.18 (6H, m), 3.06-3.17 (1H,
m), 3.39 (1H, d, J=14Hz), 3.49-3.64 (1H, m), 3.65
(1H, d, J=14Hz), 7.31 (2H, d, J=8Hz), 7.37 (1H, d,
J=8Hz), 7.46 (2H, t, J=8Hz), 7.59 (2H, d, J=8Hz),
7.65 (2H, d, J=8Hz), 9.20 (1H, s)

MS (ESI-) m/z: 358 (M-H)

Example 72

35 N-Hydroxy-2-(4-phenoxyphenyl)-1,3-dithian-2-acetamide

(88 mg)

NMR (DMSO-d₆, δ): 2.27-2.38 (2H, m), 3.43 (2H, s),
3.60-3.67 (2H, m), 3.80-3.88 (2H, m), 7.00 (2H, d,
J=8.0Hz), 7.10 (2H, d, J=8.0Hz), 7.22 (1H, dd,
J=8.0, 8.0Hz), 7.45 (2H, dd, J=8.0, 8.0Hz), 8.04
(2H, d, J=8.0Hz), 8.94 (1H, s)
MS (ESI) m/z: 360.1 (M-H)

Example 73

N-Hydroxy-2-[5-(4-chlorophenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)
NMR (DMSO-d₆, δ): 1.74-2.02 (4H, m), 2.96-3.52 (6H,
m), 7.22 (1H, d, J=3.6Hz), 7.47-7.53 (3H, m), 7.67
(2H, d, J=8.7Hz), 8.85 (1H, s), 10.59 (1H, s)
MS (ESI-) m/z: 398 (M-H)

Example 74

N-Hydroxy-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (140 mg)
NMR (DMSO-d₆, δ): 1.73-2.00 (4H, m), 2.26-2.33 (1H,
m), 2.86-2.96 (2H, m), 3.11-3.23 (2H, m), 3.40-
3.45 (1H, m), 7.03 (1H, d, J=3.9Hz), 7.22 (1H, d,
J=3.9Hz), 8.86 (1H, s), 10.57 (1H, s)
MS (ESI-) m/z: 366 (M-H)

Example 75

(2R or 2S)-N-Hydroxy-2-(5-bromo-2-thienyl)-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (65 mg) from
(2R or 2S)-N-(2-tetrahydropyranyloxy)-2-(5-bromo-2-thienyl)-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80
mg) obtained in Example 53

$[\alpha]_D^{25}$: -17.1°C (C=0.485, DMF)

NMR (DMSO-d₆, δ): 1.73-2.00 (4H, m), 2.26-2.33 (1H,
m), 2.86-2.96 (2H, m), 3.11-3.23 (2H, m), 3.40-
3.45 (1H, m), 7.03 (1H, d, J=3.9Hz), 7.22 (1H, d,

J=3.9Hz), 8.86 (1H, s), 10.57 (1H, s)

MS (ESI-) m/z: 366 (M-H)

Optical purity: 95% ee

Analytical chiral HPLC:

5 column: Chiralpak AS (4.6 x 250 mm,
Daicel Chemical Industries, Ltd.)
eluent: n-hexane-ethanol-TFA (700:300:1)
flow rate: 1.0 ml/minute
detection: 220 nm

10

The following compounds were obtained in a similar manner to that of Preparation 1-4).

Example 76

15 2-[4-(4-Fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (450 mg)

NMR (CDCl₃, δ): 1.87-2.21 (4H, m), 2.67-2.85 (2H, m),
3.03-3.15 (2H, m), 3.21 (1H, d, J=16Hz), 3.62 (1H,
d, J=16Hz), 6.94-7.04 (6H, m), 7.59 (2H, d, J=9Hz)

20 MS (ESI-) m/z: 377 (M-H)

Example 77

2-[4-(4-Bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide

25 NMR (CDCl₃, δ): 1.75-2.02 (4H, m), 2.08-2.21 (2H, m),
2.63-2.85 (2H, m), 3.02-3.16 (2H, m), 3.21 (1H, d,
J=16Hz), 3.60 (1H, d, J=16Hz), 6.92 (2H, d, J=9Hz),
7.00 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.60 (2H,
d, J=9Hz)

30 MS (ESI-) m/z: 439 (M-H)

Example 78

2-(4-Methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid

35 NMR (CDCl₃, δ): 1.71-2.00 (4H, m), 2.07-2.20 (2H, m),

2.60-2.86 (2H, m), 2.99-3.14 (2H, m), 3.19 (1H, d, J=15.5Hz), 3.60 (1H, d, J=15.5Hz), 3.81 (3H, s), 6.82 (2H, d, J=9Hz), 7.56 (2H, d, J=9Hz)

MS (ESI-) m/z: 297 (M-H)

5

Example 79

2-[5-(4-Fluorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid

10 NMR (CDCl₃, δ): 1.70-2.02 (2H, m), 2.09-2.24 (2H, m), 2.67-2.86 (2H, m), 3.02-3.20 (2H, m), 3.19 (1H, d, J=15Hz), 3.46 (1H, d, J=15Hz), 7.06 (2H, dd, J=8Hz, 8Hz), 7.15 (1H, d, J=3Hz), 7.21 (1H, d, J=3Hz), 7.46-7.62 (2H, m)

MS (ESI-) m/z: 367 (M-H)

15

Example 80

2-(4-Biphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (0.33 g)

20 NMR (CDCl₃, δ): 1.80-2.01 (2H, m), 2.11-2.19 (2H, m), 2.69-2.76 (1H, m), 2.82-2.92 (1H, m), 3.02-3.16 (2H, m), 3.24 (1H, d, J=15.6Hz), 3.67 (1H, d, J=15.6Hz), 7.37-7.46 (2H, m), 7.58-7.63 (4H, m), 7.71 (2H, d, J=9Hz)

MS (ESI-) m/z: 343 (M-H)

25

Example 81

2-[4-(4-Chlorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (275 mg)

30 NMR (CDCl₃, δ): 1.79-2.00 (2H, m), 2.10-2.18 (2H, m), 2.66-2.89 (2H, m), 3.02-3.14 (2H, m), 3.23 (1H, d, J=16Hz), 3.65 (1H, d, J=16Hz), 7.40 (2H, d, J=9Hz), 7.50 (2H, d, J=8.5Hz), 7.57 (2H, d, J=8.5Hz), 7.70 (2H, d, J=9Hz)

MS (ESI-) m/z: 377 (M-H)

35

Example 82

2-[4-(4-Bromophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (105 mg)

5 NMR (CDCl₃, δ): 1.70-2.20 (4H, m), 2.72-2.92 (2H, m),
3.05-3.16 (2H, m), 3.25 (1H, d, J=16Hz), 3.67 (1H,
d, J=16Hz), 7.44 (2H, d, J=9Hz), 7.55-7.58 (4H, m),
7.71 (2H, d, J=9Hz)

MS (ESI-) m/z: 421 (M-H)

10 Example 83

2-[4-(4-Fluorophenyl)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (220 mg)

15 NMR (CDCl₃, δ): 1.80-2.18 (4H, m), 2.69-2.91 (1H, m),
3.04-3.16 (3H, m), 3.24 (1H, d, J=16Hz), 3.66 (1H,
d, J=16Hz), 7.12 (2H, dd, J=9, 9Hz), 7.52-7.58 (4H,
m), 7.70 (2H, d, J=8.5Hz)

MS (ESI-) m/z: 361 (M-H)

Example 84

20 A mixture of 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (56 g), potassium permanganate (48.8 g) and benzyltrimethylammonium chloride (2.87 g) in water-methylene chloride (2:1, 1.5 l) was stirred for 3 hours at room temperature. After the reaction mixture
25 was poured into saturated sodium sulfite solution (500 ml), the solution was acidified with 4N hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with chloroform (400 ml x 2). The combined organic layer was washed with brine, dried over magnesium
30 sulfate and concentrated in vacuo. The resulting residue was purified with silica gel column chromatography (eluent: chloroform-methanol 10:1) to give 2-[4-(4-chlorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (17.2 g) as colorless crystal.

35 mp: 191-193°C

Example 85

N-Hydroxy-2-(4-phenoxyphenyl)-1,3-dithiane-2-acetamide
1,1,3,3-tetraoxide (56 mg) was obtained in a similar manner
5 to that of Preparation 1-4).

NMR (DMSO-d₆, δ): 2.27-2.38 (2H, m), 3.43 (2H, s),
3.60-3.67 (2H, m), 3.80-3.88 (2H, m), 7.00 (2H, d,
J=8.0Hz), 7.10 (2H, d, J=8.0Hz), 7.22 (1H, dd,
J=8.0, 8.0Hz), 7.45 (2H, dd, J=8.0, 8.0Hz), 8.04
10 (2H, d, J=8.0Hz), 8.94 (1H, s)

MS (ESI-) m/z: 424.1 (M-H)

Example 86

To a solution of 2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-
15 tetrahydro-2H-thiopyran-2-acetic acid (300 mg) in MeOH was
added dropwise titanium (III) chloride (2.67 ml) (10 wt. %
solution in hydrochloric acid) in MeOH and hydrogen peroxide
(0.69 ml) (30% aqueous solution) at room temperature. After
being stirred for 15 minutes, the reaction is stopped by
20 adding water. The reaction mixture is extracted with EtOAc
and the solution was washed with brine, dried over MgSO₄ and
concentrated in vacuo. The residue was purified by silica
gel column chromatography (eluent: 5% MeOH in CHCl₃) to
give 2-[4-(4-fluorophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-
25 thiopyran-2-acetic acid 1-oxide (150 mg) as an amorphous.

NMR (CDCl₃, δ): 1.55-1.76 (4H, m), 2.45-2.62 (4H, m),
3.05-3.07 (2H, m), 6.95-7.07 (6H, m), 7.39 (2H, d,
J=9Hz)

MS (ESI-) m/z: 361 (M-H)

Example 87

2-[5-(4-Chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetic acid 1,1-dioxide (1.95 g) was obtained in
a similar manner to that of Preparation 1-4).

35 NMR (DMSO-d₆, δ): 1.76-1.90 (4H, m), 3.16-3.55 (6H,

m), 7.19 (1H, d, J=3.6Hz), 7.47-7.52 (3H, m), 7.68 (2H, d, J=8.4Hz)

Example 88

2-(5-Bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (6.0 g) was obtained in a similar manner to that of Preparation 1-4).

NMR (DMSO-d₆, δ): 1.74-1.87 (4H, m), 2.30-2.37 (1H, m), 3.07-3.56 (5H, m), 7.02 (1H, d, J=4.2Hz), 7.21 (1H, d, J=4.2Hz)

MS (ESI-) m/z: 351 (M-H)

Example 89

A mixture of 2-[4-(4-bromophenoxy)phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (130 mg), 4-fluorobenzenboronic acid (49.7 mg) and tetrakis(triphenylphosphine)palladium(0) (3.4 mg) in a mixture of 1,2-dimethoxyethane (0.5 ml) and 2M aqueous sodium carbonate (0.5 ml) was refluxed for 6 hours. The mixture was acidified with 4N hydrochloric acid to pH 3 and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo to give 2-[4-[4-(4-fluorophenyl)phenoxy]phenyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (116 mg) as an oil.

NMR (CDCl₃, δ): 1.75-2.02 (4H, m), 2.08-2.21 (2H, m), 2.64-2.84 (2H, m), 3.01-3.17 (2H, m), 3.23 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 7.04 (2H, d, J=9Hz), 7.07-7.16 (4H, m), 7.41-7.56 (4H, m), 7.61 (2H, d, J=9Hz)

MS (ESI-) m/z: 453 (M-H)

Example 90

1.6M n-Butyl lithium in hexane (1.63 ml) was added

dropwise to a solution of diisopropylamine (261 mg) in THF (10 ml) under ice-bath cooling and a nitrogen atmosphere. After being stirred under the same condition for 30 minutes, a solution of methyl 3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide (450 mg) in THF (8 ml) was added therein and the mixture was stirred for 45 minutes under dry ice-acetone cooling. A solution of 4-phenoxybenzyl bromide (719 mg) in THF (8 ml) was added to this mixture under the same condition. After the mixture was stirred for 2 hours under the same temperature for 2 hours under ice-bath cooling and for 2 hours at room temperature, a saturated aqueous solution of ammonium chloride was added to the reaction mixture. The resulting mixture was extracted with AcOEt. The extract was washed with 5% hydrochloric acid, 1M sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel (SiO₂) column chromatography (eluent: hexane-AcOEt, 6:1) to give methyl 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide (745 mg) as an oil.

NMR (CDCl₃, δ): 1.68-1.92 (2H, m), 2.02-2.34 (4H, m), 3.10-3.30 (2H, m), 3.17 (1H, d, J=14Hz), 3.74 (1H, d, J=14Hz), 3.83 (3H, s), 6.91 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.06-7.18 (3H, m), 7.34 (2H, t, J=8Hz)

Example 91

Methyl 2-(4-phenoxybenzyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate (605 mg) was obtained in a similar manner to that of Example 90.

NMR (CDCl₃, δ): 1.46-1.82 (4H, m), 1.86-1.96 (1H, m), 2.28-2.40 (1H, m), 2.52-2.62 (1H, m), 2.69-2.80 (1H, m), 3.07 (2H, s), 3.71 (3H, s), 6.89 (2H, d, J=8Hz), 7.00 (2H, d, J=8Hz), 7.06-7.14 (3H, m), 7.33 (2H, t, J=8Hz)

Example 92

Methyl 2-(4-biphenylmethyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide (250 mg) was obtained in a similar manner to that of Preparation 90.

NMR (CDCl₃, δ): 1.72-1.93 (2H, m), 2.06-2.20 (3H, m), 2.25-2.37 (1H, m), 3.12-3.30 (2H, m), 3.24 (1H, d, J=14Hz), 3.81 (1H, d, J=14Hz), 3.86 (3H, s), 7.23 (2H, d, J=8Hz), 7.30-7.38 (1H, m), 7.43 (2H, t, J=8Hz), 7.49-7.58 (4H, m)

Example 93

To a stirred solution of ethyl 3-hydroxy-3-(4-methoxyphenyl)-7-mercaptoheptanoate (3.00 g) in dichloromethane (20 ml) was added trifluoroacetic acid (1 ml) at room temperature under nitrogen. After 1 hour, the mixture was quenched by the addition of triethylamine (1 ml) with ice cooling and concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The obtained oil was purified by column chromatography on silica gel (eluted with 5 to 10% ethyl acetate in n-hexane) to give ethyl 2-(4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (2.216 g) as an oil.

NMR (CDCl₃, δ): 1.05 (3H, t, J=7Hz), 1.50-1.84 (5H, m), 2.25-2.36 (1H, m), 2.45-2.71 (2H, m), 2.79 (1H, d, J=14Hz), 2.91 (1H, d, J=14Hz), 3.81 (3H, s), 3.93 (2H, q, J=7Hz), 6.88 (2H, d, J=9Hz), 7.55 (2H, d, J=9Hz)

Example 94

To a mixture of ethyl 3-oxo-3-(4-phenoxyphenyl)-propanoate (500 mg) and 1,3-propanedithiol (2 ml) was added

boron trifluoride diethyl etherate (2 ml) at 0°C. After being stirred at ambient temperature for 3 hours, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel 60 (50 g) (eluent: ethyl acetate:hexane (1:10)) to give ethyl 2-(4-phenoxyphenyl)-1,3-dithian-2-acetate (370 mg) as a yellow oil.

NMR (CDCl₃, δ): 1.12 (3H, t, J=7.0Hz), 1.94-2.01 (2H, m), 2.75-2.81 (4H, m), 3.13 (2H, s), 4.00 (2H, q, J=7.0Hz), 6.98 (2H, d, J=8.5Hz), 7.03 (2H, d, J=7.0Hz), 7.12 (1H, dd, J=7.0, 7.0Hz), 7.34 (2H, dd, J=7.0, 7.0Hz), 7.88 (2H, d, J=8.5Hz)

MS (ESI-) m/z: 374 (M-H)

Example 95

A mixture of tert-Butyl 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (199 g) and aqueous 90% trifluoroacetic acid (1.0 l) was stirred for 2 hours at room temperature. The mixture was diluted with water (1.5 l) and stirred for 1 hour with ice cooling. The separated solid was collected and washed with water (500 ml) to give 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid (166.2 g).

NMR (DMSO-d₆, δ): 1.45-1.73 (4H, m), 2.12-2.20 (1H, m), 2.45-2.70 (5H, m), 2.87 (1H, d, J=14.4Hz), 6.84 (1H, d, J=4.2Hz), 7.08 (1H, d, J=4.2Hz)

MS (ESI-): 319 (M-H)

Example 96

To a solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(2-(tert-butyl)(diphenyl)silyloxy)ethylaminocarbonylamino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-

acetamide 1,1-dioxide (500 mg) in tetrahydrofuran (3 ml) was added 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 ml) at 0°C and the reaction mixture was stirred at ambient temperature for 3 hours. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, 10% aqueous citric acid solution, saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel 60 (eluent: 6% methanol-chloroform) to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-((2-hydroxyethyl)-aminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg) as a white amorphous.

NMR (CDCl₃, δ): 1.46 (2H, br), 1.52-1.68 (4H, m), 1.94 (2H, br), 2.04-2.24 (2H, m), 2.67-2.88 (2H, m), 3.00-3.06 (2H, m), 3.11 (2H, m), 3.30-3.47 (2H, m), 3.72 (2H, td, J=7.0, 7.0Hz), 4.24 (2H, td, J=7.0, 7.0Hz), 4.52 (1/2H, br), 4.82 (1/2H, br), 6.80 (1H, s), 7.18-7.46 (6H, m), 7.60 (1H, s), 8.32 (1/2H, s), 8.46 (1/2H, s)

MS (ESI-): 550.5 (M-H)

Example 97

To a solution of 2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (140.0 g) in a mixture of acetonitrile (560 ml) and ethanol (800 ml) was added a solution of R-(+)-α-methylbenzylamine (28.8 g) in ethanol (40 ml) at 50°C. After been allowed to cool to ambient temperature over the time of 2 hours, the mixture was stirred for 2 hours at ambient temperature and for 2 hours with ice cooling additionally. The separated solid was collected and washed with acetonitrile (140 ml) to give (2S)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-N-[(R)-1-phenylethyl]acetamide 1,1-dioxide (66.2 g).

The absolute configuration was determined by X ray crystallography analysis.

NMR (DMSO-d₆, δ): 1.35 (3H, d, J=6.6Hz), 1.60-2.04 (4H, m), 2.18-2.32 (1H, m), 2.86-3.10 (3H, m), 3.24 (1H, d, J=15.6Hz), 3.36-3.52 (2H, m), 4.15 (1H, q, J=6.6Hz), 6.96 (1H, d, J=4.2Hz), 7.14 (1H, d, J=4.2Hz), 7.24-7.43 (5H, m)

The following compounds were obtained in substantially the same manner as that of Example 54.

Example 98

(2S)-N-Hydroxy-2-[5-(3-methylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg)

NMR (DMSO-d₆, δ): 1.75-2.06 (4H, m), 2.35 (3H, s), 2.95-3.52 (6H, m), 7.13 (1H, d, J=7.5Hz), 7.20 (1H, d, J=5Hz), 7.30 (1H, dd, J=7.5, 7.5Hz), 7.42-7.45 (3H, m), 8.84 (1H, s)

MS (ESI-): 378 (M-H)

Example 99

(2S)-N-Hydroxy-2-[5-(4-methylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (82 mg)

NMR (DMSO-d₆, δ): 1.74-2.04 (4H, m), 2.32 (3H, s), 2.47-2.53 (1H, m), 2.95-3.25 (4H, m), 3.43-3.53 (1H, m), 7.16 (1H, d, J=3.0Hz), 7.23 (2H, d, J=7.0Hz), 7.40 (1H, d, J=3.0Hz), 7.53 (2H, d, J=7.0Hz), 8.85 (1H, s)

MS (ESI-): 378.0 (M-H)

Example 100

(2S)-N-Hydroxy-2-[5-(4-ethylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (115 mg)

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.74-1.93 (2H, m),
1.96-2.16 (2H, m), 2.57-2.73 (2H, m), 2.65 (2H, q,
J=7Hz), 2.94-3.15 (4H, m), 7.14-7.24 (4H, m), 7.50
(2H, d, J=8Hz), 8.52 (1H, s)

5 MS (ESI-): 392 (M-H)

Example 101

(2S)-N-Hydroxy-2-[5-(4-methoxyphenyl)-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (970
10 mg)

NMR (DMSO-d₆, δ): 1.72-2.06 (4H, m), 2.34-2.45 (1H, m),
2.94-3.26 (4H, m), 3.39-3.56 (1H, m), 3.78 (3H, s),
6.98 (2H, d, J=7Hz), 7.16 (1H, d, J=3Hz), 7.34 (1H,
d, J=3Hz), 7.57 (2H, d, J=7Hz), 8.85 (1H, s),
15 10.58 (1H, s)

MS (ESI-): 394 (M-H)

Example 102

(2S)-N-Hydroxy-2-[5-(4-hydroxymethylphenyl)-2-thienyl]-
20 3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (75
mg)

NMR (DMSO-d₆, δ): 1.67-2.08 (4H, m), 2.33-2.48 (1H, m),
2.92-3.28 (4H, m), 3.39-3.54 (1H, m), 4.50 (2H, d,
J=6Hz), 5.24 (1H, t, J=6Hz), 7.20 (1H, d, J=3Hz),
25 7.36 (2H, d, J=7Hz), 7.44 (1H, d, J=3Hz), 7.60 (2H,
d, J=7Hz), 8.86 (1H, s)

MS (ESI-): 394 (M-H)

Example 103

30 (2S)-N-Hydroxy-2-[5-(2-thienyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (130 mg)

NMR (DMSO-d₆, δ): 1.72-2.04 (4H, m), 2.93-3.51 (6H, m),
7.10 (1H, dd, J=4.5, 4.5Hz), 7.15 (1H, d, J=4.0Hz),
7.26 (1H, d, J=4.0Hz), 7.29 (1H, d, J=4.5Hz), 7.53
35 (1H, d, J=4.5Hz), 8.32 (1H, s)

MS (ESI-): 370 (M-H)

Example 104

(2S)-N-Hydroxy-2-[5-(2-furyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (12 mg)

NMR (CDCl₃, δ): 1.80-1.97 (2H, m), 2.00-2.25 (2H, m), 2.56-2.69 (1H, m), 2.74-2.89 (1H, m), 2.96-3.20 (4H, m), 6.43-6.47 (1H, m), 6.52-6.56 (1H, m), 7.15-7.22 (2H, m), 7.39-7.44 (1H, m), 8.12 (1H, br s)

MS (ESI-): 354 (M-H)

Example 105

(2S)-N-Hydroxy-2-[5-(4-methylcarbamoylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (46 mg)

NMR (DMSO-d₆, δ): 1.68-2.10 (4H, m), 2.33-2.48 (1H, m), 2.79 (3H, d, J=4Hz), 2.92-3.32 (4H, m), 3.40-3.57 (1H, m), 7.26 (1H, d, J=3Hz), 7.60 (1H, d, J=3Hz), 7.74 (2H, d, J=8Hz), 7.88 (2H, d, J=8Hz), 8.50 (1H, m)

MS (ESI-): 421 (M-H)

Example 106

(2S)-N-Hydroxy-2-[5-(4-ethylcarbamoylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (740 mg)

NMR (DMSO-d₆, δ): 1.13 (3H, t, J=7.5Hz), 1.75-2.05 (4H, m), 2.36-2.45 (1H, m), 2.95-3.03 (2H, m), 3.13-3.47 (5H, m), 7.24 (1H, d, J=5.0Hz), 7.60 (1H, d, J=5.0Hz), 7.73 (2H, d, J=9.0Hz), 7.87 (2H, d, J=9.0Hz), 8.51 (1H, t, J=3.0Hz)

MS (ESI-): 435.2 (M-H)

35 Example 107

(2S)-N-Hydroxy-2-[5-(3-acetylamino-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide, 1,1-dioxide (2 g)

5 NMR (DMSO-d₆, δ): 1.74-2.01 (4H, m), 2.06 (3H, s),
2.35-2.46 (1H, m), 2.94-3.50 (5H, m), 7.20 (1H, d,
J=3.0Hz), 7.33 (2H, d, J=5.0Hz), 7.39 (1H, d,
J=3.0Hz), 7.44-7.49 (1H, m), 7.94 (1H, s)

MS (ESI-): 421.1 (M-H)

10 Example 108

(2S)-N-Hydroxy-2-[5-(3-amino-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (87 mg)

15 NMR (DMSO-d₆, δ): 1.69-2.09 (4H, m), 2.34-2.56 (1H, m),
2.95-3.07 (2H, m), 3.11-3.32 (2H, m), 3.40-3.57
(1H, m), 7.17 (1H, d, J=8Hz), 7.24 (1H, d, J=3Hz),
7.42-7.60 (4H, m), 10.63 (1H, s)

MS (ESI-): 379 (M-H)

20 Example 109

(2S)-N-Hydroxy-2-[5-(3-ethylcarbamoylamino-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

25 NMR (DMSO-d₆, δ): 1.06 (3H, t, J=7.2Hz), 1.69-2.09 (4H,
m), 2.31-2.53 (1H, m), 2.93-3.55 (7H, m), 6.14 (1H,
t, J=4.5Hz), 7.12-7.30 (4H, m), 7.38 (1H, d,
J=4.5Hz), 7.84 (1H, s), 8.56 (1H, s), 8.72-8.95
(1H, m), 10.60 (1H, s)

MS (ESI-): 450 (M-H)

30

Example 110

(2S)-N-Hydroxy-2-[5-(3-methoxycarbonylamino-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (82 mg)

35 NMR (DMSO-d₆, δ): 1.70-2.07 (4H, m), 2.34-2.53 (1H, m),

2.94-3.08 (2H, m), 3.10-3.27 (2H, m), 3.30-3.55
(1H, m), 3.69 (3H, s), 7.20 (1H, d, J=3.5Hz),
7.27-7.41 (4H, m), 7.83 (1H, s), 9.76 (1H, s)
MS (ESI+): 456 (M+H+NH₃)

5

Example 111

(2S)-N-Hydroxy-2-[5-(3-carbamoylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (45 mg)

10 NMR (DMSO-d₆, δ): 1.70-2.08 (4H, m), 2.32-2.55 (1H, m),
2.93-3.07 (2H, m), 3.09-3.30 (2H, m), 3.39-3.55
(1H, m), 5.90 (2H, s), 7.16-7.23 (2H, m), 7.24-
7.39 (2H, m), 7.37 (1H, d, J=3.5Hz), 7.78 (1H, s),
8.66 (1H, s), 8.84 (1H, s)

15 MS (ESI-): 422 (M-H)

Example 112

(2S)-N-Hydroxy-2-[5-(3-methylcarbamoylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (77 mg)

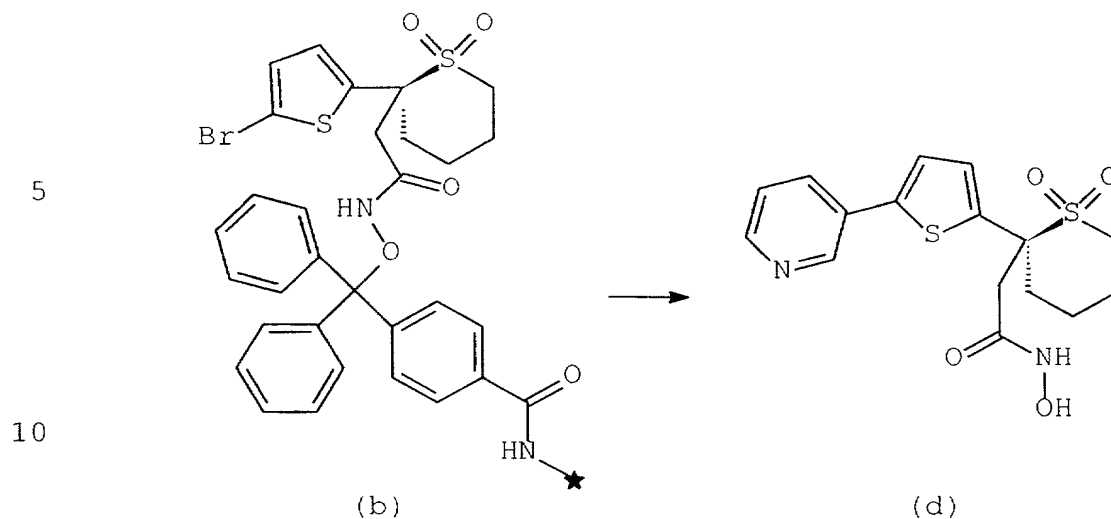
20 NMR (DMSO-d₆, δ): 1.74-2.05 (4H, m), 2.38-2.46 (1H, m),
2.66 (3H, d, J=4.0Hz), 2.95-3.26 (4H, m), 3.42-
3.52 (1H, m), 6.06 (1H, q, J=4.0Hz), 7.17-7.20 (2H,
m), 7.22-7.26 (2H, m), 7.36 (1H, d, J=3.5Hz), 7.82
25 (1H, s), 8.65 (1H, s), 8.83 (1H, s)

MS (ESI-): 436.2 (M-H)

Example 113

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35



To a solution of pyridine-3-boronic acid 1,3-propanediol cyclic ester (130 mg) in degassed N,N-dimethylformamide (0.5 ml) were added a suspension of tetrakis(triphenylphosphine)-palladium (103 mg) in degassed N,N-dimethylformamide (2.5 ml), a solution of sodium carbonate (424 mg) in degassed water (1 ml) and (2S)-N-[2-[2-(5-bromo-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]hydroxylamine trityl crowns (b) (4 mmol, 10.0 μ mol/crown) in an atmosphere of nitrogen. After resulting mixture was heated for 48 hours at 60°C, the crowns were washed with degassed N,N-dimethylformamide, a solution of sodium diethyldithiocarbamate (500 mg) and diisopropylethylamine (0.5 ml) in N,N-dimethylformamide (100 ml), N,N-dimethylformamide, methyl sulfoxide, water, methanol and dichloromethane, successively. The crowns were treated with 5% trifluoroacetic acid in dichloromethane for 1 hour at ambient temperature and removed from the solution. After the solution was evaporated under a stream of nitrogen, the residue was purified by reverse phase HPLC (0.1% trifluoroacetic acid in acetonitrile, 0-20% gradient) to give (2S)-N-hydroxy-2-[5-(3-pyridyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (10 mg) as a powder.

NMR (DMSO-d₆, δ): 1.25-2.05 (4H, m), 2.87-2.93 (1H, m),
2.97-3.50 (5H, m), 7.28 (1H, d, J=4.0Hz), 7.53-
7.58 (1H, m), 7.65 (1H, d, J=4.0Hz), 8.16 (1H, d,
J=7.5Hz), 8.56 (1H, br), 8.95 (1H, br)

5 MS (ESI-): 365.0 (M-H)

Example 114

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
methylcarbamoylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-
10 2H-thiopyran-2-acetamide 1,1-dioxide (132 mg)

NMR (CDCl₃, δ): 1.45 (4H, br), 1.62-1.66 (2H, m), 1.93
(2H, br), 2.07-2.17 (2H, m), 2.77-2.81 (5H, m),
2.98-3.03 (1H, m), 3.10-3.15 (3H, m), 3.32-3.50
(1H, m), 3.70-3.78 (1H, m), 4.59 (1Hx1/2, s), 4.83
15 (1Hx1/2, s), 7.00 (1H, d, J=3.5Hz), 7.07-7.08 (1H,
m), 7.12-7.21 (4H, m), 7.30-7.40 (2H, m), 9.16
(1Hx1/2, s), 9.35 (1Hx1/2, s)

MS (ESI-): 520.2 (M-H)

20 The following compounds were obtained in substantially
the same manner as that of Example 89.

Example 115

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-methylphenyl)-
25 2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (200 mg)

NMR (CDCl₃, δ): 1.40-1.73 (10H, m), 2.37 (3H, s), 2.69-
2.88 (2H, m), 3.06-3.16 (4H, m), 3.30-3.45 (1H, m),
3.61-3.75 (2H, m), 7.11 (1H, d, J=7.5Hz), 7.24-
30 7.28 (3H, m), 7.38-7.41 (2H, m)

Example 116

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-methylphenyl)-
2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
35 dioxide (142 mg)

NMR (CDCl₃, δ): 1.43 (2H, br), 1.65-1.69 (2H, m), 1.95 (2H, br), 2.07-2.18 (2H, m), 2.37 (3H, s), 2.63-2.80 (2H, m), 3.06 (2H, br s), 3.10-3.16 (2H, m), 3.40-3.50 (2H, m), 3.58-3.76 (2H, m), 4.53 (1Hx1/2, s), 4.80 (1Hx1/2, s), 7.15-7.24 (4H, m), 7.46 (2H, d, J=8.0Hz), 7.39 (1Hx1/2, s), 8.06 (1Hx1/2, s)
MS (ESI-): 462.1 (M-H)

Example 117

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-ethylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (CDCl₃, δ): 1.25 (3H, t, J=8Hz), 1.35-1.76 (6H, m), 1.87-2.00 (2H, m), 2.04-2.23 (2H, m), 2.60-2.91 (4H, m), 3.00-3.19 (4H, m), 3.27-3.50 (1H, m), 3.60-3.77 (1H, m), 4.53, 4.71 (1H, s), 7.15-7.28 (4H, m), 7.51 (2H, d, J=8Hz), 8.10, 8.25 (1H, s)

MS (ESI+): 478 (M+H)

Example 118

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-methoxyphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (1.85 g)

NMR (CDCl₃, δ): 1.36-1.82 (6H, m), 1.98-2.02 (2H, m), 2.10-2.25 (2H, m), 2.62-2.88 (2H, m), 2.98-3.20 (4H, m), 3.26-3.50 (1H, m), 3.57-3.72 (1H, m), 3.83 (3H, s), 6.90 (2H, d, J=8Hz), 7.13, 7.15 (1H, d, J=3Hz), 7.22, 7.24 (1H, d, J=3Hz), 7.52 (2H, d, J=8Hz), 8.11, 8.25 (1H, s)

MS (ESI-): 478 (M-H)

Example 119

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-hydroxymethylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (181 mg)

NMR (CDCl₃, δ): 1.36-1.78 (6H, m), 1.85-2.03 (2H, m),
2.06-2.55 (2H, m), 2.66-2.93 (2H, m), 2.98-3.21
(4H, m), 3.26-3.50 (1H, m), 3.62-3.73 (1H, m),
4.52, 4.82 (1H, m), 4.70 (1H, s), 7.22-7.30 (1H,
5 m), 7.35 (2H, d, J=8Hz), 7.42-7.62 (1H, m), 7.57
(2H, d, J=8Hz), 8.25, 8.35 (1H, s)

MS (ESI-): 478 (M-H)

Example 120

10 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(2-thienyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (200 mg)

NMR (CDCl₃, δ): 1.41-1.75 (10H, m), 2.65-2.82 (2H, m),
3.04-3.17 (4H, m), 3.30-3.74 (3H, m), 7.00-7.02
15 (1H, m), 7.11-7.13 (1H, m), 7.17-7.19 (3H, m)

MS (ESI-): 454 (M-H)

Example 121

20 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(2-furyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (95 mg)

NMR (CDCl₃, δ): 1.41-1.77 (6H, m), 1.85-2.00 (2H, m),
2.03-2.25 (2H, m), 2.61-2.91 (2H, m), 3.00-3.06
(2H, m), 3.07-3.16 (2H, m), 3.28-3.53 (1H, m),
25 3.61-3.75 (1H, m), 4.51 (0.5H, s), 4.80 (0.5H, s),
6.42-6.47 (1H, m), 6.50-6.56 (1H, m), 7.17-7.24
(2H, m), 7.38-7.42 (1H, m), 7.93 (0.5H, s), 8.09
(0.5H, s)

MS (ESI-): 438 (M-H)

Example 122

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-carboxyphenyl)-
2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (910 mg)

NMR (CDCl₃, δ): 1.36-1.73 (6H, m), 1.85-2.25 (4H, m),

2.76-2.88 (2H, m), 3.02-3.25 (4H, m), 3.28-3.53
(1H, m), 3.69-3.81 (1H, m), 4.56, 4.87 (1H, s),
7.57 (1H, d, J=8Hz), 7.36-7.44 (1H, m), 7.72-7.83
(2H, m), 8.00 (2H, d, J=8Hz)

5 MS (ESI-): 492 (M-H)

Example 123

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
ethylcarbamoylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
10 thiopyran-2-acetamide 1,1-dioxide (984 mg)

NMR (CDCl₃, δ): 1.28 (3H, t, J=7.0Hz), 1.44-1.55 (4H,
m), 1.64-1.68 (2H, m), 1.95 (2H, br), 2.06-2.23
(2H, m), 2.67-2.91 (2H, m), 3.01-3.16 (4H, m),
3.27-3.33 (1H, m), 3.46-3.55 (2H, m), 3.62-3.65
15 (1H, m), 4.50 (1Hx1/2, s), 4.82 (1Hx1/2, s), 7.28
(1H, d, J=4.0Hz), 7.33 (1H, d, J=4.0Hz), 7.62 (2H,
d, J=8.0Hz), 7.75 (2H, d, J=8.0Hz), 8.19 (1Hx1/2,
s), 8.27 (1Hx1/2, s)

MS (ESI-): 519.2 (M-H)

20

Example 124

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (2.63 g)

25 NMR (CDCl₃, δ): 1.43 (2H, br), 1.55-1.64 (4H, m), 1.93
(2H, br), 2.04-2.15 (2H, m), 2.19 (3H, s), 2.80-
2.85 (2H, m), 3.02-3.16 (4H, m), 3.44-3.48 (1H, m),
3.66-3.73 (1H, m), 4.55 (1Hx1/3, s), 4.85 (1Hx2/3,
s), 7.08-7.11 (1H, m), 7.16-7.23 (3H, m), 7.38 (1H,
30 br s), 7.57 (1H, d, J=7.0Hz), 7.94 (1H, s), 8.93
(1Hx1/3, s), 9.02 (1Hx2/3, s)

MS (ESI-): 505.4 (M-H)

Example 125

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-aminophenyl)-2-

thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (214 mg)

NMR (CDCl₃, δ): 1.36-1.80 (6H, m), 1.84-2.25 (4H, m),
2.61-2.92 (2H, m), 2.98-3.20 (4H, m), 3.27-3.89
(4H, m), 4.54 (0.5H, s), 4.81 (0.5H, s), 6.62 (1H,
dd, J=2.3, 8Hz), 6.91 (1H, s), 6.99 (1H, d, J=8Hz),
7.15 (1H, t, J=8Hz), 7.20-7.29 (2H, m), 7.98 (0.5H,
s), 8.15 (0.5H, s)

MS (ESI⁻): 463 (M-H)

Example 126

tert-Butyl-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetate (199 g) was obtained in substantially the same manner as that of Example 93.

NMR (CDCl₃, δ): 1.34 (9H, s), 1.46-1.91 (5H, m), 2.10-
2.22 (1H, m), 2.49-2.62 (2H, m), 2.66 (1H, d,
J=13.2Hz), 2.75 (1H, d, J=13.2Hz), 6.74 (1H, d,
J=3.9Hz), 7.45 (1H, d, J=3.9Hz)

Example 127

(2S)-2-(5-Bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-N-[(R)-1-phenylethyl]acetamide 1,1-dioxide (78 g) was partitioned between ethyl acetate (500 ml) and aqueous 1N hydrochloric acid (300 ml). The separated organic phase was washed with aqueous 1N hydrochloric acid (100 ml) and brine (100 ml), dried over sodium sulfate and concentrated in vacuo to give (2S)-2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetic acid 1,1-dioxide (57.5 g) as a solid.

mp: 189°C (dec.)

NMR (DMSO-d₆, δ): 1.74-1.87 (4H, m), 2.30-2.37 (1H, m),
3.07-3.56 (5H, m), 7.02 (1H, d, J=4.2Hz), 7.21 (1H,
d, J=4.2Hz)

Example 128

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-methylcarbamoylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (68 mg) was obtained in substantially the same manner as that of Example 32.

5 NMR (DMSO-d₆, δ): 1.35-1.64 (6H, m), 1.71-2.08 (4H, m),
2.36-2.53 (1H, m), 2.79 (3H, d, J=4Hz), 2.88-3.32
(4H, m), 3.40-3.53 (2H, m), 3.74-3.92 (1H, m),
4.45, 4.75 (1H, s), 7.22-7.30 (1H, m), 7.55-7.64
(1H, m), 7.74 (2H, d, J=8Hz), 7.88 (2H, d, J=8Hz),
10 8.50 (1H, d, J=4Hz), 11.25 (1H, s)

MS (ESI-): 505 (M-H)

Example 129

To a mixture of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-aminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg) in dichloromethane (1.5 ml) was added a solution of ethylisocyanate (21.9 mg) in dichloromethane (0.5 ml) with ice cooling. The mixture was allowed to warm to room temperature and stirred for 3 hours.
20 The resulted mixture was purified by chromatography on silica gel (methanol in chloroform, 0.5 to 3% gradient) to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-ethylcarbamoylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg) as an amorphous
25 solid.

NMR (CDCl₃, δ): 1.08-1.18 (3H, m), 1.38-1.75 (6H, m),
1.86-2.00 (2H, m), 2.02-2.24 (2H, m), 2.76-2.90
(2H, m), 2.96-3.17 (4H, m), 3.20-3.55 (3H, m),
3.70-3.85 (1H, m), 4.61 (0.5H, s), 4.84 (0.5H, s),
30 5.25-5.40 (1H, m), 6.95-7.34 (5H, m), 7.36-7.50
(1H, m), 9.13 (0.5H, s), 9.35 (0.5H, s)

MS (ESI-): 534 (M-H)

Example 130

35 To a mixture of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-

(3-aminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg) and pyridine (28.1 mg) in dichloromethane (1.5 ml) was added a solution of methyl chloroformate (26.8 mg) in dichloromethane (0.5 ml) with ice cooling. The mixture was allowed to warm to room temperature and stirred for 3 hours. The resulted mixture was washed with aqueous 0.5% citric acid and brine, dried over sodium sulfate and concentrated in vacuo. The obtained residue was purified by chromatography on silica gel (methanol in chloroform, 0.5 to 3% gradient) to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-methoxycarbonylamino-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (101 mg) as an amorphous solid.

NMR (CDCl₃, δ): 1.35-1.56 (4H, m), 1.59-1.75 (2H, m), 1.86-2.00 (2H, m), 2.05-2.26 (2H, m), 2.63-2.93 (2H, m), 3.01-3.17 (4H, m), 3.27-3.51 (1H, m), 3.58-3.74 (1H, m), 3.79 (3H, s), 4.54 (0.5H, s), 4.82 (0.5H, s), 6.74 (1H, br s), 7.15-7.21 (1H, m), 7.23-7.37 (4H, m), 7.62 (1H, br s), 8.10 (0.5H, s), 8.24 (0.5H, s)

MS (ESI-): 521 (M-H)

The following compound was obtained in substantially the same manner as that of Example 129.

Example 131

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-aminocarbamoylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (170 mg)

NMR (DMSO-d₆, δ): 1.36-1.65 (6H, m), 1.69-2.10 (4H, m), 2.34-2.48 (1H, m), 2.89-3.32 (4H, m), 3.39-3.54 (2H, m), 3.72-3.91 (1H, m), 4.43 (0.5H, s), 4.75 (0.5H, s), 5.90 (2H, s), 7.16-7.30 (4H, m), 7.32-7.49 (1H, m), 7.79 (1H, s), 8.66 (1H, s)

MS (ESI-): 506 (M-H)

Example 132

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-fluorophenyl)-
2-thienyl]-2,3,4,5-tetrahydrothiophene-2-acetamide 1,1-
dioxide (272 mg) was obtained in a similar manner to that of
Example 32.

NMR (CDCl₃, δ): 1.39-1.84 (6H, m), 2.27-2.41 (2H, m),
2.82-3.00 (4H, m), 3.13-3.25 (2H, m), 3.35-3.63
(1H, m), 3.68-3.80 (1H, m), 4.55-4.64 (0.5H, m),
4.81-4.89 (0.5H, m), 7.03-7.11 (2H, m), 7.13-7.40
(2H, m), 7.49-7.58 (2H, m), 8.20 (0.5H, s), 8.30
(0.5H, s)

MS (ESI-): 452 (M-H)

The following compounds were obtained in substantially
the same manner as that of Example 54.

Example 133

(2S)-N-Hydroxy-2-[5-(3-ethoxyacetylaminophenyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (4.62 g)

NMR (DMSO-d₆, δ): 1.20 (3H, t, J=7Hz), 2.35-2.48 (1H,
m), 2.94-3.28 (4H, m), 3.42-3.53 (1H, m), 3.58 (2H,
q, J=7Hz), 4.04 (2H, s), 7.21 (1H, d, J=3Hz),
7.32-7.44 (3H, m), 7.57-7.63 (1H, m), 8.03 (1H, s),
8.85 (1H, br), 9.81 (1H, s)

MS (ESI-): 465 (M-H)

Example 134

(2S)-N-Hydroxy-2-[5-(3-propionylaminophenyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (76 mg)

NMR (DMSO-d₆, δ): 1.09 (3H, t, J=7Hz), 2.35 (2H, q,
J=7Hz), 2.37-2.48 (1H, m), 2.90-3.52 (5H, m), 7.21

(1H, d, J=3Hz), 7.28-7.53 (5H, m), 8.00 (1H, s),
9.98 (1H, s), 10.61 (1H, s)

MS (ESI-): 435 (M-H)

5 Example 135

(2S)-N-Hydroxy-2-[5-(3-propylaminocarbonylaminophenyl)-
2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (75 mg)

10 NMR (DMSO-d₆, δ): 0.88 (3H, t, J=7Hz), 1.44 (2H, q,
J=7Hz), 1.68-2.10 (4H, m), 2.34-2.48 (1H, m),
2.90-3.58 (7H, m), 6.22 (1H, br), 7.11-7.30 (4H,
m), 7.48 (1H, d, J=3Hz), 7.84 (1H, s), 8.60 (1H,
s), 10.61 (1H, s)

MS (ESI-): 464 (M-H)

15

Example 136

(2S)-N-Hydroxy-2-[5-(3-butyrylaminophenyl)-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (79
mg)

20 NMR (DMSO-d₆, δ): 0.92 (3H, t, J=7Hz), 1.55-1.68 (2H,
m), 1.69-2.10 (4H, m), 2.30 (2H, t, J=7Hz), 2.35-
2.48 (1H, m), 2.92-3.65 (5H, m), 7.20 (1H, d,
J=3Hz), 7.34 (2H, d, J=3Hz), 7.40 (1H, d, J=3Hz),
7.44-7.53 (1H, m), 8.00 (1H, s)

25 MS (ESI-): 449 (M-H)

Example 137

(2S)-N-Hydroxy-2-[5-(3-(2-methoxyethoxycarbonylamino)-
phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
30 acetamide 1,1-dioxide (64 mg)

NMR (DMSO-d₆, δ): 1.70-2.11 (4H, m), 2.34-2.50 (1H, m),
2.92-3.26 (4H, m), 3.29 (3H, s), 3.40-3.66 (3H, m),
4.15-4.28 (2H, m), 7.20 (1H, d, J=3Hz), 7.26-7.42
(4H, m), 7.85 (1H, s), 8.84 (1H, s), 9.87 (1H, s),
35 10.60 (1H, s)

MS (ESI-): 481 (M-H)

Example 138

(2S)-N-Hydroxy-2-[5-(3-(2-methoxycarbonylaminoacetyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (58 mg)

NMR (DMSO-d₆, δ): 1.69-2.07 (4H, m), 2.32-2.48 (1H, m),
2.92-3.50 (5H, m), 3.56 (3H, s), 3.80 (2H, d, J=8Hz), 7.19 (1H, d, J=3Hz), 7.30-7.52 (5H, m),
7.97 (1H, s), 8.82 (1H, s)

MS (ESI-): 494 (M-H)

Example 139

(2S)-N-Hydroxy-2-[5-(3-(phenoxyacetyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.8 g)

NMR (DMSO-d₆, δ): 1.70-2.09 (4H, m), 2.35-2.50 (1H, m),
2.92-3.55 (5H, m), 4.72 (2H, s), 6.94-7.05 (3H, m),
7.21 (1H, d, J=3Hz), 7.28-7.44 (5H, m), 7.52-7.60 (1H, m), 8.03 (1H, s), 8.84 (1H, s), 10.21 (1H, s),
10.60 (1H, s)

MS (ESI-): 513 (M-H)

Example 140

(2S)-N-Hydroxy-2-[5-(3-(propoxyacetyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (2.28 g)

NMR (DMSO-d₆, δ): 0.91 (3H, t, J=8Hz), 1.54-1.67 (2H, m), 1.70-2.11 (4H, m), 2.36-2.49 (1H, m), 2.94-3.29 (4H, m), 3.43-3.58 (1H, m), 3.48 (2H, t, J=8Hz), 4.05 (2H, s), 7.21 (1H, d, J=3Hz), 7.32-7.45 (3H, m), 7.54-7.62 (1H, m), 8.03 (1H, s), 8.85 (1H, s), 9.81 (1H, s), 10.60 (1H, s)

MS (ESI-): 479 (M-H)

Example 141

(2S)-N-Hydroxy-2-[5-[3-(2-propen-1-yloxy)acetylaminophenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (9.32 g)

5 NMR (DMSO-d₆, δ): 1.70-2.09 (4H, m), 2.35-2.56 (1H, m),
2.94-3.08 (2H, m), 3.10-3.29 (2H, m), 3.30-3.55
(1H, m), 4.07 (2H, s), 4.10 (2H, d, J=6Hz), 5.22
(1H, d, J=9Hz), 5.34 (1H, d, J=15Hz), 5.89-6.04
(1H, m), 7.21 (1H, d, J=3.5Hz), 7.31-7.44 (3H, m),
10 7.55-7.61 (1H, m), 8.03 (1H, s), 8.85 (1H, br s),
9.86 (1H, s), 10.6 (1H, br s)

MS (ESI-): 477 (M-H)

Example 142

15 (2S)-N-Hydroxy-2-[5-[4-(5-oxazolyl)phenyl]-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (331
mg)

NMR (DMSO-d₆, δ): 1.72-2.10 (4H, m), 2.36-2.49 (1H, m),
2.95-3.09 (2H, m), 3.11-3.30 (2H, m), 3.42-3.56
20 (1H, m), 7.24 (1H, d, J=3.9Hz), 7.57 (1H, d,
J=3.9Hz), 7.76 (1H, s), 7.77 (4H, s), 8.48 (1H, s)

MS (ESI-): 431 (M-H)

Example 143

25 (2S)-N-Hydroxy-2-[5-{3-(n-butyloxyacetylaminophenyl)}-
2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (90 mg)

NMR (DMSO-d₆, δ): 0.92 (3H, t, J=7.0Hz), 1.47 (2H, tq,
J=7.0, 7.0Hz), 1.60 (2H, dd, J=7.0, 7.0Hz), 1.74-
30 2.06 (4H, m), 2.37-2.47 (1H, m), 2.96-3.30 (4H, m),
3.38-3.45 (1H, m), 3.52 (2H, t, J=7.0Hz), 4.05 (2H,
s), 7.22 (1H, d, J=4.0Hz), 7.32-7.37 (2H, m), 7.41
(1H, d, J=4.0Hz), 7.55-7.60 (1H, m), 8.02 (1H, s),
8.84 (1H, s), 9.80 (1H, s), 10.59 (1H, s)

35 MS (ESI-): 493.2 (M-H)

Example 144

(2S)-N-Hydroxy-2-[5-{3-ethoxycarbonylaminoacetylaminophenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (2.3 g)

NMR (DMSO-d₆, δ): 1.18 (3H, t, J=7.0Hz), 1.74-2.05 (4H, m), 2.36-2.46 (1H, m), 2.95-3.26 (4H, m), 3.40-3.53 (1H, m), 3.79 (2H, d, J=6.0Hz), 4.02 (2H, q, J=7.0Hz), 7.21 (1H, d, J=4.0Hz), 7.35-7.40 (3H, m), 7.40 (1H, d, J=4.0Hz), 7.45-7.49 (1H, m), 7.97 (1H, s), 8.84 (1H, s), 10.08 (1H, s)

MS (ESI-): 508.3 (M-H)

Example 145

(2S)-N-Hydroxy-2-[5-{3-(2-chloroethylaminocarbonylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (72 mg)

NMR (DMSO-d₆, δ): 1.72-2.04 (4H, m), 2.36-2.45 (1H, m), 2.93-3.23 (4H, m), 3.39-3.46 (3H, m), 3.67 (2H, t, J=6.0Hz), 6.44 (1H, t, J=6.0Hz), 7.17-7.30 (4H, m), 7.38 (1H, d, J=4.0Hz), 7.84 (1H, s), 8.81 (1H, s), 8.84 (1H, s)

MS (ESI-): 484.3 (M-H)

Example 146

(2S)-N-Hydroxy-2-[5-{3-(3-methoxypropionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.4 g)

NMR (DMSO-d₆, δ): 1.72-2.05 (4H, m), 2.38-2.47 (1H, m), 2.56 (2H, t, J=6.0Hz), 2.95-3.21 (4H, m), 3.27 (3H, s), 3.36-3.52 (1H, m), 3.64 (2H, t, J=6.0Hz), 7.20 (1H, d, J=4.0Hz), 7.31-7.36 (2H, m), 7.40 (1H, d, J=4.0Hz), 7.45-7.49 (1H, m), 8.01 (1H, s), 10.07 (1H, s), 10.60 (1H, s)

MS (ESI-): 479.2 (M-H+Na)

Example 147

(2S)-N-Hydroxy-2-[5-{3-(methoxyacetyl-amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (2.5 g)

NMR (DMSO-d₆, δ): 1.74-2.06 (4H, m), 2.37-2.48 (1H, m),
2.95-3.26 (4H, m), 3.41 (3H, s), 3.43-3.53 (1H, m),
4.02 (2H, s), 7.20 (1H, d, J=4.0Hz), 7.32-7.38 (2H,
m), 7.42 (1H, d, J=4.0Hz), 7.58-7.63 (1H, m), 8.04
(1H, s), 8.84 (1H, s), 9.87 (1H, s), 10.60 (1H, s)

MS (ESI-): 451.2 (M-H)

Example 148

(2S)-N-Hydroxy-2-[5-(3-hydroxymethylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (60 mg)

NMR (DMSO-d₆, δ): 1.71-2.08 (4H, m), 2.37-2.46 (1H, m),
2.95-3.54 (5H, m), 4.54 (2H, d, J=5.5Hz), 5.29 (1H,
dd, J=5.5, 5.5Hz), 7.21 (1H, d, J=4.0Hz), 7.25 (1H,
d, J=8.0Hz), 7.38 (1H, dd, J=8.0, 8.0Hz), 7.46 (1H,
d, J=4.0Hz), 7.53 (1H, d, J=8.0Hz), 7.59 (1H, s),
8.85 (1H, s), 10.6 (1H, s)

MS (ESI-): 394 (M-H)

Example 149

(2S)-N-Hydroxy-2-[5-(4-(cis-1,2-dihydroxyethyl)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

NMR (DMSO-d₆, δ): 1.73-2.07 (4H, m), 2.35-2.46 (1H, m),
2.95-3.50 (5H, m), 4.51-4.56 (1H, m), 4.70-4.80
(1H, br), 5.24-5.35 (1H, br), 7.20 (1H, d,
J=4.0Hz), 7.39 (2H, d, J=8.0Hz), 7.44 (1H, d,
J=4.0Hz), 7.58 (2H, d, J=8.0Hz), 8.83 (1H, s),
10.58 (1H, s)

MS (ESI-): 424 (M-H)

Example 150

(2S)-N-Hydroxy-2-[5-(3-(methylaminocarbonyloxymethyl)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-

5 acetamide 1,1-dioxide (100 mg)

NMR (DMSO-d₆, δ): 1.70-2.06 (4H, m), 2.35-2.46 (1H, m),
2.59 (3H, d, J=5.0Hz), 2.96-3.54 (5H, m), 5.05 (2H,
m), 7.22 (1H, d, J=4.0Hz), 7.29 (1H, d, J=8.0Hz),
7.42 (1H, dd, J=8.0, 8.0Hz), 7.49 (1H, d, J=4.0Hz),
10 7.59-7.61 (2H, m), 8.84 (1H, br), 10.59 (1H, br)

MS (ESI-): 451 (M-H)

Example 151

(2S)-N-Hydroxy-2-[5-(4-(2-methylaminocarbonyl-ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (170 mg)

NMR (DMSO-d₆, δ): 1.72-2.09 (4H, m), 2.38-2.48 (1H, m),
2.71 (3H, d, J=5Hz), 2.98-3.51 (5H, m), 6.63 (1H,
d, J=15Hz), 7.23 (1H, d, J=4Hz), 7.42 (1H, d,
20 J=15Hz), 7.55 (1H, d, J=4Hz), 7.60 (2H, d,
J=8.4Hz), 7.69 (2H, d, J=8.4Hz), 8.05 (1H, d,
J=5Hz), 10.60 (1H, s)

MS (ESI-): 447 (M-H)

Example 152

(2S)-N-Hydroxy-2-[5-(4-(2-ethylaminocarbonylethyl)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)

NMR (DMSO-d₆, δ): 1.08 (3H, t, J=7.2Hz), 1.73-2.12 (4H,
30 m), 2.39-2.48 (1H, m), 2.96-3.05 (2H, m), 3.11-
3.54 (5H, m), 6.63 (1H, d, J=15Hz), 7.24 (1H, d,
J=4Hz), 7.41 (1H, d, J=15Hz), 7.55 (1H, d, J=4Hz),
7.60 (2H, d, J=8.4Hz), 7.69 (2H, d, J=8.4Hz), 8.10
(1H, dd, J=7.2, 7.2Hz), 10.6 (1H, s)

35 MS (ESI-): 461 (M-H)

Example 153

(2S)-N-Hydroxy-2-[5-(3-(isopropylaminocarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-

5 acetamide 1,1-dioxide (82 mg)

NMR (DMSO-d₆, δ): 1.10 (6H, d, J=8Hz), 1.65-2.11 (4H, m), 2.30-2.45 (1H, m), 2.85-3.26 (4H, m), 3.36-3.56 (1H, m), 3.65-3.88 (1H, m), 6.08 (1H, br s), 7.07-7.45 (6H, m), 7.84 (1H, s), 8.50 (1H, s),
10 10.62 (1H, s)

MS (ESI-): 464 (M-H)

Example 154

(2S)-N-Hydroxy-2-[5-[3-[(2-hydroxyethylamino)-acetylaminophenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (82 mg)

NMR (DMSO-d₆, δ): 1.70-2.10 (4H, m), 2.32-2.53 (1H, m), 2.94-3.06 (2H, m), 3.09-3.20 (2H, m), 3.21-3.30 (2H, m), 3.40-3.88 (3H, m), 3.98-4.05 (2H, m),
20 7.23 (1H, d, J=3.5Hz), 7.37-7.53 (4H, m), 7.93-8.00 (2H, m), 8.93-9.07 (2H, s)

MS (ESI+): 482 (M+H)

Example 155

(2S)-N-Hydroxy-2-[5-[3-[(4-morpholino)acetylaminophenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (75 mg)

NMR (DMSO-d₆, δ): 1.70-2.10 (4H, m), 2.32-2.52 (1H, m), 2.90-3.06 (2H, m), 3.09-3.37 (4H, m), 3.41-3.58 (5H, m), 3.62-4.03 (2H, m), 4.25 (2H, s), 7.23 (1H, d, J=3.5Hz), 7.40-7.54 (5H, m), 8.03 (1H, s)

MS (ESI+): 508 (M+H)

Example 156

(2S)-N-Hydroxy-2-[5-(3-(4-methoxyphenyl)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-

phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (105 mg)

NMR (DMSO-d₆, δ): 1.70-2.08 (4H, m), 2.34-2.48 (1H, m),
2.92-3.30 (4H, m), 3.42-3.54 (1H, m), 3.58 (2H, s),
3.73 (3H, s), 6.90 (2H, d, J=9Hz), 7.20 (1H, d,
J=3Hz), 7.26 (2H, d, J=9Hz), 7.32-7.38 (2H, m),
7.40 (1H, d, J=3Hz), 7.44-7.53 (1H, m), 7.99 (1H,
s), 8.84 (1H, br s), 10.24 (1H, s), 10.60 (1H, s)

MS (ESI-): 527 (M-H)

Example 157

(2S)-N-Hydroxy-2-[5-(3-(3-methoxyphenoxy)acetylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg)

NMR (DMSO-d₆, δ): 1.68-2.11 (4H, m), 2.32-2.50 (1H, m),
2.90-3.66 (5H, m), 4.71 (2H, s), 6.49-6.66 (2H, m),
7.13-7.26 (2H, m), 7.31-7.47 (2H, m), 7.52-7.72
(2H, m), 7.94-8.14 (1H, m), 8.70 (2H, br s), 10.23
(1H, s), 10.62 (1H, s)

MS (ESI-): 543 (M-H)

Example 158

(2S)-N-Hydroxy-2-[5-(3-(3-phenoxypropionylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (78 mg)

NMR (DMSO-d₆, δ): 1.69-2.12 (4H, m), 2.35-2.50 (1H, m),
2.82 (2H, t, J=7Hz), 2.92-3.56 (5H, m), 4.28 (2H,
t, J=7Hz), 6.95 (3H, d, J=9Hz), 7.21 (1H, d,
J=3Hz), 7.29 (2H, t, J=8Hz), 7.34-7.55 (4H, m),
8.03 (1H, s), 8.84 (1H, s), 10.21 (1H, s), 10.60
(1H, s)

MS (ESI-): 527 (M-H)

Example 159

(2S)-N-Hydroxy-2-[5-(3-(4-fluorophenoxy)acetylamino)-

phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (75 mg)

5 NMR (DMSO-d₆, δ): 1.69-2.11 (4H, m), 2.34-2.49 (1H, m),
2.92-3.56 (5H, m), 4.71 (2H, s), 6.97-7.36 (5H, m),
7.83-7.46 (3H, m), 7.52-7.62 (1H, m), 8.02 (1H, s),
8.84 (1H, s), 10.20 (1H, s), 10.60 (1H, s)
MS (ESI-): 531 (M-H)

Example 160

10 (2S)-N-Hydroxy-2-[5-(3-(4-methoxyphenoxy)acetylamino)-
phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (89 mg)

15 NMR (DMSO-d₆, δ): 1.68-2.08 (4H, m), 2.35-2.50 (1H, m),
2.94-3.30 (4H, m), 3.41-3.54 (1H, m), 3.70 (3H, s),
4.65 (2H, s), 6.90 (2H, d, J=10Hz), 6.98 (2H, d,
J=10Hz), 7.21 (1H, d, J=3Hz), 7.33-7.45 (3H, m),
7.54-7.62 (1H, m), 8.03 (1H, s), 8.84 (1H, s),
10.17 (1H, s), 10.60 (1H, s)
20 MS (ESI-): 543 (M-H)

Example 161

(2S)-N-Hydroxy-2-[5-(3-(2-(methylaminocarbonyloxy)-
acetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (68 mg)

25 NMR (DMSO-d₆, δ): 1.64-2.08 (4H, m), 2.32-2.51 (1H, m),
2.61 (3H, s), 2.92-3.56 (5H, m), 4.57 (2H, s),
7.12-7.54 (7H, m), 7.98 (1H, s), 10.14 (1H, s),
10.61 (1H, s)
30 MS (ESI-): 494 (M-H)

Example 162

(2S)-N-Hydroxy-2-(5-phenyl-2-thienyl)-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (51 mg)

NMR (DMSO-d₆, δ): 1.70-2.07 (4H, m), 2.34-2.52 (1H, m),

2.94-3.07 (2H, m), 3.10-3.27 (2H, m), 3.30-3.50
(1H, m), 7.21 (1H, d, J=3.5Hz), 7.29-7.36 (1H, m),
7.43 (2H, t, J=8Hz), 7.48 (1H, d, J=3.5Hz), 7.65
(2H, d, J=8Hz), 8.85 (1H, br s)

5 MS (ESI-): 364 (M-H)

Example 163

(2S)-N-Hydroxy-2-[5-(4-ethylaminocarbonylmethoxy)-
phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
10 acetamide 1,1-dioxide (35 mg)

NMR (DMSO-d₆, δ): 1.04 (3H, t, J=7.2Hz), 1.71-2.08 (4H,
m), 1.35-1.45 (1H, m), 2.95-3.50 (7H, m), 4.89 (2H,
s), 7.00 (2H, d, J=9.0Hz), 7.17 (1H, d, J=4.0Hz),
7.35 (1H, d, J=4.0Hz), 7.58 (2H, d, J=9.0Hz), 8.12
15 (1H, br), 8.84 (1H, s), 10.59 (1H, s)

Example 164

(2S)-N-Hydroxy-2-[5-(4-(methylaminocarbonylmethoxy)-
phenyl)-2-thienyl]-3,4,5,6-tettrarahydro-2H-thiopyran-2-
20 acetamide 1,1-dioxide (450 mg)

NMR (DMSO-d₆, δ): 1.70-2.07 (4H, m), 2.35-2.45 (1H, m),
2.65 (3H, d, J=4.5Hz), 2.95-3.50 (5H, m), 4.50 (2H,
s), 7.01 (2H, d, J=9.0Hz), 7.16 (1H, d, J=4.0Hz),
7.35 (1H, d, J=4.0Hz), 7.57 (2H, d, J=9.0Hz), 8.06
25 (1H, br), 8.84 (1H, s), 10.57 (1H, s)

MS (ESI-): 451 (M-H)

Example 165

(2S)-N-Hydroxy-2-[5-(4-fluorophenyl)-2-thienyl]-
30 2,3,4,5-tetrahydrothiophene-2-acetamide 1,1-dioxide (200 mg)

NMR (DMSO-d₆, δ): 2.14-2.35 (2H, m), 2.55-2.68 (1H, m),
2.80 (1H, d, J=15Hz), 2.90 (1H, d, J=15Hz), 3.05-
3.40 (3H, m), 7.17 (1H, d, J=4Hz), 7.26 (2H, d,
J=9Hz), 7.45 (1H, d, J=4Hz), 7.70 (2H, dd, J=5,
35 9Hz), 8.88 (1H, s), 10.60 (1H, s)

MS (ESI-): 368 (M-H)

Example 166

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(acetoxycetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg) was dissolved in 50% trifluoroacetic acid in dichloromethane (10 ml) and the reaction mixture was stirred at room temperature for 1 hour. After the mixture was concentrated in vacuo, the residue was purified by SiO₂ column chromatography (eluent: 2% MeOH in CHCl₃) to afford (2S)-N-hydroxy-2-[5-(3-(acetoxycetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (65 mg) as a powder.

NMR (DMSO-d₆, δ): 1.69-2.07 (4H, m), 2.14 (3H, s), 2.32-2.47 (1H, m), 2.92-3.55 (5H, m), 4.67 (2H, s), 7.22 (1H, d, J=3Hz), 7.32-7.52 (3H, m), 7.97 (1H, s)

MS (ESI-): 479 (M-H)

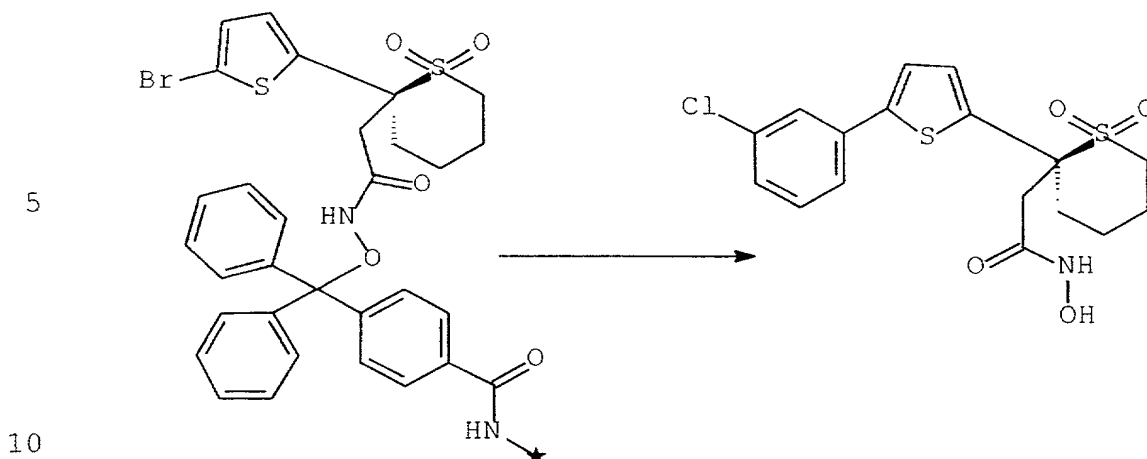
Example 167

(2S)-N-Hydroxy-2-[5-(3-((2S)-2-acetoxypionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (50 mg)

NMR (DMSO-d₆, δ): 1.44 (3H, d, J=8Hz), 1.72-2.08 (4H, m), 2.33-2.49 (1H, m), 2.93-3.32 (4H, m), 3.40-3.56 (1H, m), 5.04 (1H, q, J=8Hz), 7.22 (1H, d, J=3Hz), 7.32-7.53 (4H, m), 7.97 (1H, s), 8.84 (1H, s), 10.19 (1H, s), 10.59 (1H, s)

MS (ESI-): 493 (M-H)

Example 168



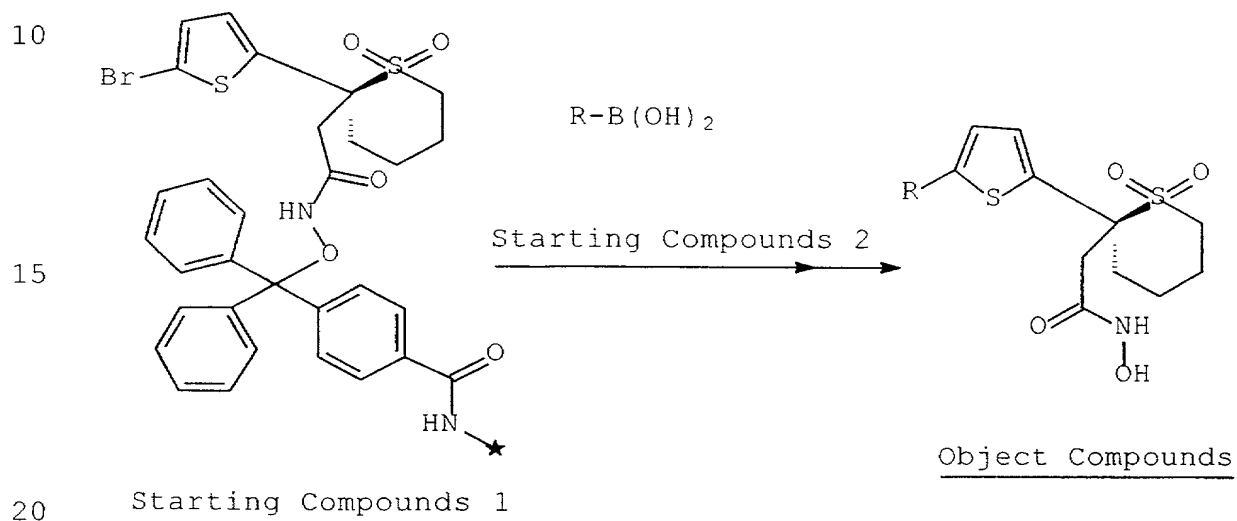
To a solution of 3-chlorophenylboronic acid (125 mg) in degassed N,N-dimethylformamide (0.5 ml) was added a suspension of tetrakis(triphenylphosphine)palladium (103 mg) in degassed N,N-dimethylformamide (2.5 ml), a solution of sodium carbonate (424 mg) in degassed water (1 ml) and N-[2-[2-(5-bromo-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]hydroxylamine trityl crowns (59.2 μ mol, 14.8 μ mol/crown) in an atmosphere of nitrogen. After resulting mixture was heated for 48 hours at 60°C, the crowns were washed with degassed N,N-dimethylformamide, a solution of sodium diethylditiocarbamate (500 mg) and diisopropylethylamine (0.5 ml) in N,N-dimethylformamide (100 ml), N,N-dimethylformamide, methyl sulfoxide, water, methanol and dichloromethane, successively. The crowns were treated with 5% trifluoroacetic acid in dichloromethane for 1 hour at ambient temperature and removed from the solution. After the solution was evaporated under a stream of nitrogen, the residue was purified by HPLC (0.1% trifluoroacetic acid in 30% ethanol-hexane) to give (2S)-N-hydroxy-2-[5-(3-chlorophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (4.5 mg) as a powder.

MS (ESI+): 400.2 (M+H)

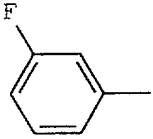
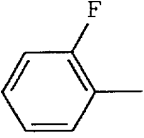
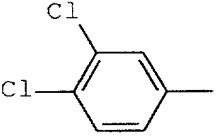
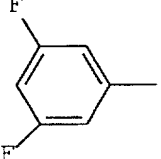
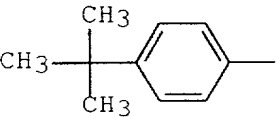
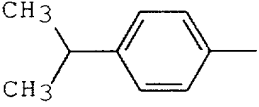
The Object Compounds listed in the Table were obtained from the Starting Compounds 1 and 2 in a similar manner to that of Example 168 according to the following reaction scheme.

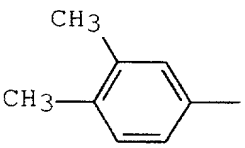
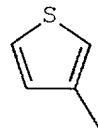
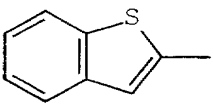
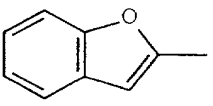
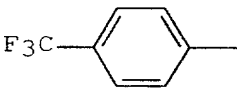
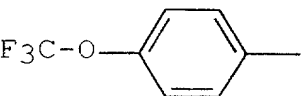
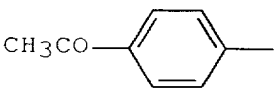
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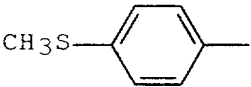
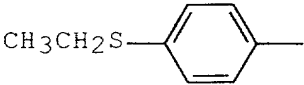
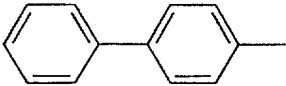
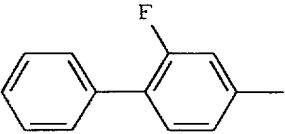
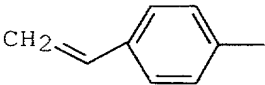
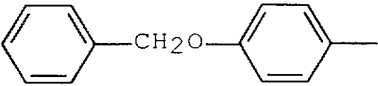
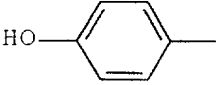
Reaction Scheme: (Examples 169 to 190)

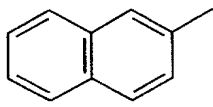
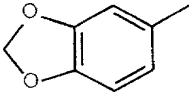


Table

Example Nos.	Object Compounds	
	R	Physicochemical Data
169		MS (ESI+): 384.3 (M+H)
170		MS (ESI+): 384.3 (M+H)
171		MS (ESI+): 434.2 (M+H)
172		MS (ESI+): 402.2 (M+H)
173		MS (ESI+): 422.4 (M+H)
174		MS (ESI+): 408.2 (M+H)

Example Nos.	Object Compounds	
	R	Physicochemical Data
175		MS (ESI+): 394.2 (M+H)
176		MS (ESI+) 372.2 (M+H)
177		MS (ESI+): 422.2 (M+H)
178		MS (ESI-): 568.4 (M-H)
179		MS (ESI+): 434.3 (M+H)
180		MS (ESI+): 450.2 (M+H)
181		MS (ESI+): 408.3 (M+H) (2R or 2S)

Example Nos.	Object Compounds	
	R	Physicochemical Data
182		MS (ESI+): 412.3 (M+H)
183		MS (ESI+): 426.2 (M+H)
184		MS (ESI+): 442.3 (M+H)
185		MS (ESI+): 501.2 (M+H)
186		MS (ESI-): 568.4 (M-H)
187		MS (ESI+): 513.3 (M+H+CH ₃ CN)
188		MS (ESI+): 382.3 (M+H) (2R or 2S)

Example Nos.	Object Compounds	
	R	Physicochemical Data
189		MS (ESI+): 416.3 (M+H)
190		MS (ESI+): 410.3 (M+H)

The following compounds were obtained in a similar manner to that of Example 54.

5 Example 191

(2S)-N-Hydroxy-2-[5-(3-aminoacetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (3.0 g) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(2-(t-butoxycarbonylamino)-acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.68-2.10 (4H, m), 2.34-2.48 (1H, m), 2.92-3.62 (5H, m), 3.76-3.88 (2H, m), 7.23 (1H, d, J=3Hz), 7.36-7.46 (3H, m), 7.49-7.56 (1H, m), 7.99 (1H, s), 10.69 (1H, s), 10.92 (1H, s)

MS (ESI+): 438 (M+H)

Example 192

(2S)-N-Hydroxy-2-[5-(3-(3-(N-methylamino)-propionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (112 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(3-(N-t-butoxycarbonyl-N-methylamino)propionylamino)phenyl)-2-

thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

5 NMR (DMSO-d₆, δ): 1.68-2.11 (4H, m), 2.32-2.47 (1H, m),
2.61 (3H, t, J=4Hz), 2.78 (2H, t, J=7Hz), 2.90-
3.30 (6H, m), 3.38-3.62 (1H, m), 7.22 (1H, d,
J=3Hz), 7.32-7.50 (4H, m), 8.04 (1H, s), 8.36-8.58
(2H, m), 10.33 (1H, s), 10.61 (1H, s)
MS (ESI+): 466 (M+H)

10 Example 193

(2S)-N-Hydroxy-2-[5-{3-((2S)-2-amino-3-(3-pyridyl)propionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (500 mg) from (2S)-N-(2-tetrahydropyranyloxy)-
15 2-[5-{3-((2S)-2-(t-butoxycarbonylamino)-3-(3-pyridyl)propionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

20 NMR (DMSO-d₆, δ): 1.74-2.06 (4H, m), 2.35-2.46 (1H, m),
2.97-3.34 (4H, m), 3.46-3.55 (3H, m), 4.24 (1H, br), 7.23 (1H, d, J=4.0Hz), 7.41-7.44 (3H, m),
7.56 (1H, d, J=7.0Hz), 7.88 (1H, dd, J=7.0, 7.0Hz),
7.95 (1H, s), 8.38 (1H, d, J=7.0Hz), 8.48 (2H, br),
8.77 (1H, br), 8.87 (1H, br s)
MS (ESI+): 529.1 (M+H)

25

Example 194

(2S)-N-Hydroxy-2-[5-(3-(2-(N-methylamino)acetyl amino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (78 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(2-(N-t-butoxycarbonylamino)-acetyl amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

35 NMR (DMSO-d₆, δ): 1.65-2.08 (4H, m), 2.31-2.49 (1H, m), 2.63 (2H, t, J=7Hz), 2.92-3.52 (5H, m), 3.92-4.00 (2H, m), 7.23 (1H, d, J=3Hz), 7.34-7.45 (3H,

m), 7.49-7.57 (1H, m), 7.98 (1H, s), 8.97-9.14 (2H, m), 10.67 (1H, s), 10.94 (1H, s)

MS (ESI+): 454 (M+H)

5 Example 195

(2S)-N-Hydroxy-2-[5-(3-(3-aminopropionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (78 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(3-(t-butoxycarbonylamino)-propionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.68-2.09 (4H, m), 2.32-2.50 (1H, m), 2.78 (2H, d, J=8Hz), 2.92-3.62 (7H, m), 7.23 (1H, d, J=3Hz), 7.32-7.57 (4H, m), 7.92-8.16 (4H, m), 10.45 (1H, s), 10.67 (1H, s)

MS (ESI+): 454 (M+H)

Example 196

(2S)-N-Hydroxy-2-[5-[3-(((2S)-2-amino-3-methoxypropionyl)amino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (1.64 g) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-[3-(((2S)-2-(t-butoxycarbonylamino)-3-methoxypropionyl)amino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.70-2.10 (4H, m), 2.34-2.53 (1H, m), 2.94-3.06 (2H, m), 3.10-3.56 (6H, m), 3.74-3.86 (2H, m), 4.17-4.29 (1H, m), 7.22 (1H, d, J=3.5Hz), 7.38-7.46 (3H, m), 7.53-7.59 (1H, m), 7.95 (1H, s), 8.30-8.44 (2H, m), 8.84 (1H, br s), 10.63 (1H, s), 10.85 (1H, br s)

MS (ESI+): 482 (M+H)

Example 197

(2S)-N-Hydroxy-2-[5-(3-(2-hydroxyacetyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (58 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(2-methoxycarbonyloxyacetyl-amino)phenyl)-2-thienyl]-

5 3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.70-2.12 (4H, m), 2.32-2.49 (1H, m),
2.91-3.28 (4H, m), 3.39-3.55 (1H, m), 4.01 (2H, d, J=7Hz), 5.71 (1H, t, J=7Hz), 7.22 (1H, d, J=3Hz),
7.38-7.40 (2H, m), 7.40 (1H, d, J=3Hz), 7.60-7.72
10 (1H, m), 8.08 (1H, s), 8.85 (1H, s), 9.79 (1H, s),
10.61 (1H, s)

MS (ESI-): 437 (M-H)

Example 198

15 (2S)-N-Hydroxy-2-[5-(3-(((2S)-2-hydroxypropionyl)-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (65 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(((2S)-2-acetoxypropionyl)amino)phenyl)-2-thienyl]-3,4,5,6-
20 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.33 (3H, br s), 1.67-2.12 (4H, m),
2.30-2.48 (1H, m), 2.90-3.71 (5H, m), 4.09-4.24
(1H, m), 7.21 (1H, br s), 7.38-7.48 (3H, m), 7.68-
7.75 (1H, m), 8.11 (1H, s), 9.26 (1H, s), 10.60
25 (1H, s)

MS (ESI-): 451 (M-H)

Example 199

To a solution of (2S)-N-2-(tetrahydropyranyloxy)-2-[5-(3-(3-aminopropionylamino)phenyl)-2-thienyl]-3,4,5,6-
30 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (180 mg) in chloroform (5 ml) and pyridine (1 ml) was added a solution of methoxycarbonyl chloride (38.1 mg) at room temperature. After being stirred at the same temperature overnight, the
35 mixture was concentrated in vacuo. The residue was

dissolved in ethyl acetate (10 ml) and the solution was washed successively with a 5% citric acid solution, a saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. After the
5 residue was dissolved in 1% hydrogen chloride in methanol (5 ml), the mixture was stirred at room temperature for 15 minutes and concentrated in vacuo. The residue was purified by SiO₂ column chromatography (eluent: 2% MeOH in CHCl₃) to afford (2S)-N-hydroxy-2-[5-(3-(3-
10 (methoxycarbonylamino)propionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (63 mg) as a powder.

NMR (DMSO-d₆, δ): 1.22-2.11 (4H, m), 2.35-2.56 (3H, m),
2.94-3.33 (6H, m), 3.42-3.58 (1H, m), 7.20 (1H, d,
15 J=3Hz), 7.21-7.38 (1H, m), 7.32-7.38 (2H, m), 7.40 (1H, d, J=3Hz), 7.42-7.50 (1H, m), 8.01 (1H, s),
8.85 (1H, m)

MS (ESI-): 508 (M-H)

20 Example 200

To a solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-(t-butyloxycarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg) in tetrahydrofuran (THF):H₂O= 2:1 (3 ml) was added lithium
25 hydroxide monohydrate (23.9 mg) at room temperature. After being stirred at the same temperature overnight, the reaction mixture was concentrated in vacuo. The resulting residue was diluted with ethyl acetate, washed with 1% citric acid solution and brine, dried over sodium sulfate
30 and concentrated in vacuo to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-carboxymethoxyphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (190 mg) as an amorphous solid.

NMR (DMSO-d₆, δ): 1.35-1.60 (6H, m), 1.66-1.71 (2H, m),

1.73-2.05 (2H, m), 2.34-2.46 (1H, m), 2.90-3.50
(6H, m), 3.72-3.90 (1H, m), 4.45, 4.75 (1H, s),
4.72 (2H, s), 6.96 (2H, d, J=9.0Hz), 7.16 (1H, d,
J=4.0Hz), 7.32 (1H, d, J=4.0Hz), 7.56 (2H, d,
J=9.0Hz), 11.2 (1H, s)

MS (ESI-): 522 (M-H)

Example 201

To the reaction mixture of 4-(5-oxazolyl)-
benzeneboronic acid pinacol cyclic ester obtained in
Preparation 24-2) was added (2S)-N-(2-tetrahydropyranyloxy)-
2-(5-bromo-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (679 mg),
tetrakis(triphenylphosphine)palladium(0) (8.67 mg) and
aqueous 2M sodium carbonate (7.5 ml) at room temperature.
The mixture was stirred for 3 hours at 80°C and taken up
between ethyl acetate and 3% aqueous sodium bicarbonate.
The separated organic layer was washed with brine, dried
over sodium sulfate and evaporated in vacuo. The residue
was purified by chromatography on silica gel (eluted with
0.5 to 3% methanol in chloroform) to give (2S)-N-(2-
tetrahydropyranyloxy)-2-[5-[4-(5-oxazolyl)phenyl]-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide
1,1-dioxide (795 mg) as an amorphous solid.

NMR (CDCl₃, δ): 1.40-1.55 (4H, m), 1.61-1.75 (2H, m),
1.91-2.02 (2H, m), 2.05-2.25 (2H, m), 2.70-2.94
(2H, m), 3.01-3.17 (4H, m), 3.29-3.51 (1H, m),
3.64-3.74 (1H, m), 4.53 (0.5Hz, s), 4.82 (0.5H, s),
7.26-7.34 (2H, m), 7.39 (1H, s), 7.65 (4H, s),
7.94 (1H, s), 8.25 (0.5H, s), 8.37 (0.5H, s)

MS (ESI-): 515 (M-H)

The following compounds were obtained in a similar
manner to that of Example 89.

Example 202

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-formylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (0.9 g)

5 NMR (CDCl₃, δ): 1.40-1.75 (6H, m), 1.90-2.02 (2H, m),
2.05-2.26 (2H, m), 2.70-2.93 (2H, m), 3.01-3.19 (2H,
m), 3.28-3.53 (1H, m), 3.62-3.75 (1H, m), 4.53,
4.83 (1H, s), 7.26-7.37 (2H, m), 7.56 (1H, dd,
J=8.0, 8.0Hz), 7.80-7.85 (2H, m), 8.09 (1H, s),
10 10.05 (1H, s)

MS (ESI-): 476 (M-H)

Example 203

15 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-ethenylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (2.1 g)

20 NMR (CDCl₃, δ): 1.37-1.75 (6H, m), 1.86-2.00 (2H, m),
2.05-2.25 (2H, m), 2.65-2.91 (2H, m), 3.00-3.17
(4H, m), 3.26-3.49 (1H, m), 3.59-3.70 (1H, m),
4.51, 4.81 (1H, s), 5.28 (1H, d, J=11Hz), 5.78 (1H,
d, J=17.7Hz), 6.66-6.75 (1H, m), 7.41 (2H, d,
J=8.0Hz), 7.55 (2H, d, J=8.0Hz)

MS (ESI-): 474 (M-H)

Example 204

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-carboxyethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (1.1 g)

30 NMR (CDCl₃, δ): 1.41-1.71 (6H, m), 1.92-2.25 (4H, m),
2.76-2.88 (2H, m), 3.05-3.19 (4H, m), 3.30-3.51
(1H, m), 3.69-3.76 (1H, m), 4.54, 4.84 (1H, s),
6.40 (1H, d, J=15Hz), 7.45-7.74 (7H, m)

MS (ESI-): 518 (M-H)

Example 205

(2S)-N-(2-Tetrahydropyranyloxy)-2-(5-phenyl-2-thienyl)-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (93
mg)

NMR (CDCl₃, δ): 1.39-1.75 (6H, m), 1.90-2.00 (2H, m),
2.04-2.24 (2H, m), 2.63-2.91 (2H, m), 3.03-3.18
(4H, m), 3.27-3.50 (1H, m), 3.59-3.70 (1H, m),
4.53 (0.5H, s), 4.80 (0.5H, s), 7.24-7.41 (5H, m),
7.56-7.63 (2H, m), 7.95 (0.5H, s), 8.12 (0.5H, s)

MS (ESI-): 448 (M-H)

Example 206

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(t-
butyloxycarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.8 g)

NMR (DMSO-d₆, δ): 1.35-1.60 (15H, m), 1.65-1.71 (2H,
m), 1.73-2.04 (2H, m), 2.34-2.45 (1H, m), 2.90-
3.50 (6H, m), 3.72-3.90 (1H, m), 4.45, 4.75 (1H,
s), 4.73 (2H, s), 7.01 (2H, d, J=9.0Hz), 7.15 (1H,
d, J=4.0Hz), 7.33 (1H, d, J=4.0Hz), 7.55 (2H, d,
J=9.0Hz)

Example 207

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
(ethylaminocarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (65 mg) was
obtained in a similar manner to that of Example 201.

NMR (DMSO-d₆, δ): 1.04 (3H, t, J=7.2Hz), 1.37-1.63 (6H,
m), 1.69-1.81 (2H, m), 1.83-2.04 (2H, m), 2.35-
2.47 (1H, m), 2.87-3.51 (8H, m), 3.74-3.90 (1H, m),
3.95, 4.75 (1H, s), 4.49 (2H, s), 7.00 (2H, d,
J=9.0Hz), 7.15-7.20 (1H, m), 7.33-7.36 (1H, m),
7.58 (2H, d, J=9.0Hz), 8.13 (1H, br)

Example 208

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-

(propylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (140 mg)

NMR (DMSO-d₆, δ): 0.88 (3H, t, J=7Hz), 1.26-2.09 (12H, m), 2.43-2.46 (1H, m), 2.78-3.56 (6H, m), 3.72-3.92 (1H, m), 4.44, 4.75 (1H, s), 6.11-6.24 (1H, m), 7.09-7.42 (6H, m), 7.85 (1H, s), 8.55 (1H, s)

MS (ESI-): 548 (M-H)

The following compounds were obtained in a similar manner to that of Example 129.

Example 209

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(isopropylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

NMR (DMSO-d₆, δ): 1.10 (6H, m), 1.30-2.10 (10H, m), 2.34-2.47 (1H, m), 2.83-3.30 (5H, m), 3.40-3.53 (1H, m), 3.18-3.90 (2H, m), 4.36, 4.44 (1H, s), 6.04 (1H, d, J=8Hz), 7.09-7.40 (6H, m), 7.85 (1H, s), 8.44 (1H, s)

MS (ESI-): 548 (M-H)

Example 210

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-chloroethylaminocarbonylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (335 mg)

NMR (CDCl₃, δ): 1.46 (2H, br), 1.62-1.67 (4H, m), 1.84-1.96 (2H, m), 2.74-2.88 (2H, m), 2.96-3.06 (2H, m), 3.08-3.14 (2H, m), 3.31-3.41 (2H, m), 3.49-3.54 (1H, m), 3.55-3.60 (2H, m), 3.66 (2H, t, J=6.0Hz), 3.70-3.80 (1H, m), 4.48 (1/2H, br), 4.84 (1/2H, br), 7.17-7.24 (4H, m), 7.30-7.50 (5H, m)

MS (ESI-): 568.4 (M-H)

Example 211

To a solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-aminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (7.00 g), ethoxyacetic acid (2.04 g) and 1-hydroxybenzotriazole (2.65 g) in N,N-dimethylformamide (80 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSCD HCl) (3.75 g) at room temperature. After being stirred at the same temperature overnight, the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (200 ml) and the solution was washed successively with 5% citric acid solution, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by SiO₂ column chromatography (eluent 1% MeOH in CHCl₃) to afford (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(2-ethoxyacetyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (7.00 g).

NMR (DMSO-d₆, δ): 1.20 (3H, t, J=7Hz), 1.33-1.62 (6H, m), 1.70-2.12 (4H, m), 2.35-2.50 (1H, m), 2.88-3.22 (5H, m), 3.38-3.52 (1H, m), 3.58 (2H, q, J=7Hz), 3.75-3.92 (1H, m), 4.44, 4.75 (1H, s), 7.18-7.25 (1H, m), 7.34-7.45 (3H, m), 7.55-7.64 (1H, m), 8.03 (1H, s), 9.81 (1H, s), 11.24 (1H, s)

MS (ESI-): 549 (M-H)

The following compounds were obtained in substantially the same manner as that of Example 211.

Example 212

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(methylaminocarbonyloxy)acetyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (144 mg)

NMR (DMSO-d₆, δ): 1.36-2.10 (10H, m), 2.36-2.51 (1H,

m), 2.60 (3H, d, J=6Hz), 2.87-3.30 (5H, m), 3.40-3.54 (1H, m), 3.72-3.90 (1H, m), 4.43, 4.76 (1H, m), 4.57 (2H, s), 7.18-7.30 (2H, m), 7.35-7.52 (4H, m), 7.99 (1H, s), 10.14 (1H, s), 11.25 (1H, s)

5 MS (ESI-): 578 (M-H)

Example 213

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[3-((2S)-2-(tert-butoxycarbonylamino)-3-methoxypropionylamino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (2.90 g)

10 NMR (CDCl₃, δ): 1.37-1.51 (11H, m), 1.59-2.01 (6H, m), 2.04-2.25 (2H, m), 2.64-2.91 (2H, m), 3.00-3.17 (4H, m), 3.26-3.50 (4H, m), 3.53-3.72 (2H, m), 3.80-3.94 (1H, m), 4.34-4.45 (1H, m), 4.53 (0.5H, s), 4.82 (0.5H, s), 5.45-5.59 (1H, m), 7.20-7.36 (5H, m), 7.43-7.51 (1H, m), 7.75-7.83 (1H, m), 8.18 (0.5H, s), 8.31 (0.5H, s), 8.49 (1H, br s)

15 MS (ESI+): 683 (M+H+NH₃)

20

Example 214

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(4-methoxyphenyl)acetyl amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

25 NMR (CDCl₃, δ): 1.36-1.76 (8H, m), 1.86-1.98 (2H, m), 2.04-2.22 (2H, m), 2.69-2.92 (2H, m), 3.02-3.17 (2H, m), 3.26-3.51 (1H, m), 3.62-3.73 (1H, m), 3.68 (2H, s), 3.82 (3H, s), 4.52, 4.72 (1H, s), 6.87-6.95 (2H, m), 7.13-7.32 (6H, m), 7.45-7.56 (3H, m), 8.56, 8.59 (1H, s)

30

MS (ESI-): 611 (M-H)

Example 215

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(tert-butoxycarbonylamino)acetyl amino)phenyl)-2-thienyl]-3,4,5,6-

tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (246 mg)

NMR (DMSO-d₆, δ): 1.26-1.63 (6H, m), 1.40 (9H, s),
1.68-2.06 (4H, m), 2.35-2.48 (1H, m), 2.88-3.30
(5H, m), 3.36-3.53 (1H, m), 3.74 (2H, d, J=7Hz),
3.72-3.92 (1H, m), 4.43, 4.75 (1H, s), 7.03-7.12
(1H, m), 7.18-7.24 (1H, m), 7.40-7.53 (4H, m),
7.98 (1H, s), 10.05 (1H, s), 11.25 (1H, s)

MS (ESI-): 620 (M-H)

10 Example 216

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-propoxyacetyl-amino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.68 g)

NMR (CDCl₃, δ): 1.01 (3H, t, J=7Hz), 1.36-1.78 (10H, m),
1.88-1.99 (2H, m), 2.03-2.25 (2H, m), 2.65-2.93
(2H, m), 2.98-3.18 (2H, m), 3.28-3.52 (1H, m),
3.58 (2H, t, J=7Hz), 3.62-3.74 (1H, m), 4.07 (2H,
s), 4.52, 4.82 (1H, s), 7.23-7.38 (4H, m), 7.52-
7.59 (1H, m), 7.80 (1H, s), 8.19, 8.32 (1H, s),
8.56 (1H, s)

MS (ESI-): 563 (M-H)

Example 217

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(n-butyl-
oxyacetyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-
2H-thiopyran-2-acetamide 1,1-dioxide (140 mg)

NMR (CDCl₃, δ): 1.95 (2H, br), 2.08-2.23 (2H, m), 2.64-
2.88 (2H, m), 3.06 (2H, s), 3.16 (2H, br), 3.39-
3.50 (2H, m), 3.62 (2H, t, J=7.5Hz), 4.06 (2H, s),
4.54 (1/2H, br), 4.80 (1/2H, br), 7.21-7.30 (2H,
m), 7.34-7.36 (2H, m), 7.52-7.56 (1H, m), 7.80 (1H,
s), 7.94 (1/2H, s), 8.12 (1/2H, s), 8.34 (1H, s)

MS (ESI-): 577.3 (M-H)

35 Example 218

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(3-methoxypropionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (4.34 g)

NMR (CDCl₃, δ): 1.46 (2H, br), 1.57-1.70 (2H, m), 1.95 (2H, br), 2.07-2.20 (2H, m), 2.66 (2H, t, J=6.0Hz), 2.70-2.89 (2H, m), 3.06 (2H, s), 3.10-3.16 (2H, m), 3.26-3.44 (1H, m), 3.47 (3H, s), 3.62-3.70 (2H, m), 3.75 (2H, t, J=6.0Hz), 4.52 (1/2H, br), 4.82 (1/2H, br), 7.20-7.25 (2H, m), 7.28-7.31 (2H, m), 7.46-7.51 (1H, m), 7.70-7.73 (1H, m), 8.18 (1/2H, s), 8.31 (1/2H, s), 8.31 (1H, s)

MS (ESI-): 549.4 (M-H)

Example 219

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(methoxyacetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.24 g)

NMR (CDCl₃, δ): 1.46 (4H, br), 1.55-1.58 (2H, m), 1.94 (2H, br), 2.07-2.20 (2H, m), 2.66-2.88 (2H, m), 3.05 (2H, s), 3.09-3.14 (2H, m), 3.27-3.48 (1H, m), 3.53 (3H, s), 3.60-3.72 (1H, m), 4.04 (2H, s), 4.52 (1/2H, br), 4.81 (1/2H, br), 7.23-7.30 (2H, m), 7.43-7.46 (2H, m), 7.55-7.59 (1H, m), 7.80 (1H, s), 8.04 (1/2H, s), 8.20 (1/2H, s), 8.30 (1H, s)

MS (ESI-): 535.3 (M-H)

Example 220

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(3-(9-fluorenylmethoxycarbonylamino)propionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (2.70 g)

NMR (CDCl₃, δ): 1.31-1.81 (8H, m), 1.84-2.28 (4H, m), 2.58-2.76 (2H, m), 2.92-3.22 (4H, m), 3.30-3.84 (4H, m), 4.02-4.22 (2H, m), 4.37-4.49 (1H, m), 4.62, 4.94 (1H, s), 6.89-7.90 (13H, m), 7.99-8.14

(2H, m), 8.66, 8.78 (1H, s), 10.00, 10.46 (1H, s)
MS (ESI-): 756 (M-H)

Example 221

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-phenoxyacetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (4.90 g)

NMR (CDCl₃, δ): 1.37-1.76 (8H, m), 1.88-1.99 (2H, m),
2.05-2.26 (2H, m), 2.67-2.92 (2H, m), 2.98-3.18
(2H, m), 3.28-3.51 (1H, m), 3.62-3.75 (1H, m),
4.62 (2H, s), 4.52, 4.82 (1H, s), 6.98-7.11 (3H, m),
7.23-7.30 (2H, m), 7.32-7.40 (4H, m), 7.58-
7.62 (1H, m), 7.79 (1H, s), 8.24, 8.35 (1H, s),
8.36 (1H, s)

MS (ESI-): 597 (M-H)

Example 222

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(3-methoxyphenoxy)acetylaminophenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (140 mg)

NMR (DMSO-d₆, δ): 1.34-1.77 (8H, m), 1.86-1.99 (2H, m),
2.05-2.24 (2H, m), 2.66-2.90 (2H, m), 3.03-3.17
(2H, m), 3.28-3.52 (1H, m), 3.62-3.74 (1H, m),
3.82 (3H, s), 4.52, 4.82 (1H, s), 4.61 (2H, s),
6.52-6.65 (3H, m), 7.22-7.30 (3H, m), 7.33-7.42
(2H, m), 7.55-7.62 (1H, m), 7.72-7.82 (1H, m),
8.26-8.42 (2H, m)

MS (ESI-): 627 (M-H)

Example 223

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(3-phenoxypropionylaminophenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (135 mg)

NMR (CDCl₃, δ): 1.32-1.78 (8H, m), 1.86-1.98 (2H, m),
2.06-2.25 (2H, m), 2.71-2.92 (2H, m), 2.86 (2H, t),

J=7Hz), 3.01-3.20 (2H, m), 3.28-3.52 (1H, m),
3.63-3.77 (1H, m), 4.35 (2H, t, J=7Hz), 4.54, 4.84
(1H, s), 6.78-7.03 (4H, m), 7.12-7.36 (5H, m),
7.47-7.65 (2H, m), 8.13 (1H, s), 8.73 (1H, s)

5 MS (ESI-): 644 (M-H)

Example 224

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(4-
fluorophenoxy)acetylamino)phenyl)-2-thienyl]-3,4,5,6-
10 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (158 mg)
NMR (CDCl₃, δ): 1.35-2.01 (10H, m), 2.05-2.23 (2H, m),
2.66-2.94 (2H, m), 3.01-3.19 (2H, m), 3.29-3.53
(1H, m), 3.62-3.26 (1H, m), 4.53, 4.82 (1H, s),
4.58 (2H, s), 6.92-7.10 (5H, m), 7.24-7.39 (3H, m),
15 7.56-7.62 (1H, m), 7.73-7.77 (1H, m), 8.34 (1H, s),
8.39, 8.49 (1H, s)
MS (ESI-): 615 (M-H)

Example 225

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(4-
methoxyphenoxy)acetylamino)phenyl)-2-thienyl]-3,4,5,6-
20 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)
NMR (CDCl₃, δ): 1.36-1.78 (8H, m), 1.87-2.01 (2H, m),
2.06-2.26 (2H, m), 2.65-2.94 (2H, m), 3.02-3.23
25 (2H, m), 3.27-3.56 (1H, m), 3.62-3.36 (1H, m),
3.80 (3H, s), 4.52, 4.83 (1H, s), 4.57 (2H, s),
6.84-7.03 (4H, m), 7.24-7.43 (4H, m), 7.54-7.67
(1H, m), 7.80 (1H, s), 8.28-8.49 (2H, m)
MS (ESI-): 627 (M-H)

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Example 226

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(3-(N-tert-
butoxycarbonyl-N-methylamino)propionylamino)phenyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
35 dioxide (160 mg)

NMR (CDCl₃, δ): 1.38-1.75 (8H, m), 1.48 (9H, s), 1.88-2.01 (2H, m), 2.06-2.24 (2H, m), 2.62-2.88 (4H, m), 2.91 (3H, s), 3.02-3.17 (2H, m), 3.27-3.50 (1H, m), 3.58-3.75 (3H, m), 4.53, 4.32 (1H, s), 7.18-7.31 (6H, m), 7.52-7.59 (1H, m), 7.70-7.83 (1H, m)

MS (ESI-): 648 (M-H)

Example 227

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-((2S)-2-(tert-butoxycarbonylamino)-3-(3-pyridyl)propionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (1.54 g)

NMR (DMSO-d₆, δ): 1.22-1.27 (2H, m), 1.43 (9H, s), 1.63-1.68 (4H, m), 1.98 (2H, br), 2.07-2.25 (2H, m), 2.74-2.98 (2H, m), 3.04-3.20 (6H, m), 3.41-3.48 (1H, m), 3.66-3.76 (1H, m), 4.45 (1/2H, br), 4.54-4.63 (1H, br), 4.86 (1/2H, br), 5.31-5.45 (1H, m), 6.82-7.00 (2H, m), 7.04-7.20 (3H, m), 7.22-7.27 (2H, m), 7.52-7.65 (2H, m), 8.43-8.59 (3H, m)

MS (ESI+): 713.1 (M+H)

Example 228

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[3-[2-(2-propen-1-yloxy)acetyl]aminophenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (14.6 g)

NMR (CDCl₃, δ): 1.37-1.76 (6H, m), 1.88-2.01 (2H, m), 2.04-2.26 (2H, m), 2.64-2.92 (2H, m), 3.00-3.17 (4H, m), 3.27-3.51 (1H, m), 3.61-3.72 (1H, m), 4.08 (2H, s), 4.16 (2H, d, J=6Hz), 4.52 (0.5H, s), 4.81 (0.5H, s), 5.33 (1H, d, J=9Hz), 5.37 (1H, d, J=16.5Hz), 5.90-6.04 (1H, m), 7.23-7.39 (5H, m), 7.53-7.60 (1H, m), 7.80 (1H, s), 8.16 (0.5H, s), 8.22 (0.5H, s), 8.35 (1H, s)

MS (ESI-): 561 (M-H)

Example 229

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(ethoxycarbonylamino)acetylaminophenyl)-2-thienyl}]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (4 g)

5 NMR (CDCl₃, δ): 1.28 (3H, t, J=7.5Hz), 1.41 (2H, br),
1.92 (2H, br), 2.04-2.17 (2H, m), 2.55 (4H, br),
2.73-2.91 (2H, m), 3.02-3.13 (4H, m), 3.28-3.49
(1H, m), 3.64-3.74 (1H, m), 4.03-4.05 (2H, m),
4.20 (2H, q, J=7.5Hz), 4.52 (1/2H, br), 4.83 (1/2H,
10 br), 7.11-7.21 (3H, m), 7.37-7.43 (1H, m), 7.48-
7.56 (2H, m), 7.74-7.80 (1H, m), 8.46 (1H, br)
MS (ESI-): 628.2 (M-H+Cl)

Example 230

15 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(N-tert-butoxycaronyl-N-methylamino)acetylaminophenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (119 mg)

20 NMR (CDCl₃, δ): 1.35-1.74 (8H, m), 1.51 (9H, s),
1.88-2.00 (2H, m), 2.05-2.55 (2H, m), 2.18-2.92
(2H, m), 3.03 (3H, s), 3.05-3.16 (2H, m), 3.28-
3.50 (1H, m), 3.62-3.76 (1H, m), 3.99 (2H, s),
4.53, 4.83 (1H, s), 7.22-7.34 (4H, m), 7.43 (1H,
br s), 7.67-7.85 (1H, m), 8.42, 8.50 (1H, s)
25 MS (ESI-): 634 (M-H)

Example 231

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(3-(tert-butoxycaronylamino)propionylaminophenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

30 NMR (CDCl₃, δ): 1.35-1.72 (8H, m), 1.44 (9H, s),
1.88-2.01 (2H, m), 2.05-2.23 (2H, m), 2.57-2.67
(2H, m), 2.75-2.89 (2H, m), 3.00-3.17 (4H, m),
35 3.28-3.56 (3H, m), 3.65-3.76 (1H, m), 4.54, 4.84

(1H, s), 5.28 (1H, br s), 7.13-7.28 (4H, m), 7.48-7.66 (2H, m), 8.14 (1H, br s), 8.75, 8.78 (1H, s)
MS (ESI-): 634 (M-H)

5 The following compounds were obtained in a similar manner to that of Example 130.

Example 232

10 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(propionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

15 NMR (DMSO-d₆, δ): 1.09 (3H, t, J=7Hz), 1.32-2.07 (10H, m), 2.36 (2H, q, J=7Hz), 2.37-2.47 (1H, m), 2.88-3.22 (5H, m), 3.35-3.54 (1H, m), 3.74-3.92 (1H, m), 4.44, 4.75 (1H, s), 7.17-7.25 (1H, m), 7.30-7.42 (3H, m), 7.43-7.52 (1H, m), 8.00 (1H, s), 9.98 (1H, s), 11.36 (1H, s)

MS (ESI-): 519 (M-H)

20 Example 233

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(butyrylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (166 mg)

25 NMR (CDCl₃, δ): 1.01 (3H, t, J=7Hz), 1.35-1.84 (10H, m), 2.05-2.25 (2H, m), 2.37 (2H, t, J=7Hz), 2.66-2.92 (2H, m), 2.97-3.17 (2H, m), 3.27-3.52 (1H, m), 3.60-3.77 (1H, m), 4.54, 4.74 (1H, s), 7.08-7.32 (5H, m), 7.48-7.66 (2H, m), 8.64 (1H, br)

MS (ESI-): 533 (M-H)

30 Example 234

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-methoxyethoxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg)

35 NMR (CDCl₃, δ): 1.37-1.78 (8H, m), 1.89-2.00 (2H, m),

2.05-2.25 (2H, m), 2.67-2.94 (2H, m), 3.02-3.18
(3H, m), 3.26-3.52 (1H, m), 3.58-3.69 (2H, m),
3.66 (3H, s), 4.25-4.32 (2H, m), 4.52, 4.83 (1H,
s), 6.90-7.00 (1H, m), 7.20-7.32 (5H, m), 7.63 (1H,
s), 8.34, 8.46 (1H, s)

MS (ESI-): 565 (M-H)

Example 235

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(9-fluorenylmethoxycarbonylamino)acetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (486 mg)

NMR (DMSO-d₆, δ): 1.34-1.62 (6H, m), 1.71-2.08 (4H, m), 2.36-2.47 (1H, m), 2.88-3.34 (5H, m), 3.39-3.52 (2H, m), 3.74-3.92 (3H, m), 4.19-4.37 (3H, m), 4.42, 4.77 (1H, s), 7.18-7.27 (1H, m), 7.32-7.52 (7H, m), 7.62-7.70 (1H, m), 7.75 (2H, d, J=7Hz), 7.92 (2H, d, J=7Hz), 8.02 (1H, s)

Example 236

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(acetoxycetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (260 mg)

NMR (CDCl₃, δ): 1.35-1.77 (8H, m), 1.86-2.00 (2H, m), 2.03-2.24 (2H, m), 2.71-2.92 (2H, m), 3.00-3.20 (2H, m), 3.38-3.54 (1H, m), 3.65-3.78 (1H, m), 4.52, 4.72 (1H, s), 4.72 (2H, s), 7.14-7.35 (4H, m), 7.52, 7.59 (1H, s), 7.56-7.67 (1H, m), 8.06-8.15 (1H, m), 8.59-8.70 (1H, m)

MS (ESI-): 563 (M-H)

Example 237

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-((2S)-2-acetoxypionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (313 mg)

NMR (CDCl₃, δ): 1.38-1.78 (8H, m), 1.49, 1.57 (3H, d, J=8Hz), 1.88-2.00 (2H, m), 2.07-2.22 (2H, m), 2.72-2.92 (2H, m), 3.03-3.19 (2H, m), 3.29-3.56 (1H, m), 3.64-3.78 (1H, m), 4.53, 4.82 (1H, s), 5.06, 5.34 (1H, q, J=8Hz), 7.18-7.36 (4H, m), 7.53-7.68 (2H, m), 8.10 (1H, br s), 8.55, 8.59 (1H, s)

MS (ESI-): 577 (M-H)

10 Example 238

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(chloroacetyl amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (201 mg)

NMR (CDCl₃, δ): 1.40-1.54 (4H, m), 1.60-1.73 (2H, m), 1.88-2.00 (2H, m), 2.06-2.25 (2H, m), 2.67-2.91 (2H, m), 3.02-3.18 (4H, m), 3.29-3.51 (1H, m), 3.62-3.75 (1H, m), 4.21 (2H, s), 4.53 (0.5H, s), 4.82 (0.5H, s), 7.23-7.29 (2H, m), 7.32-7.41 (2H, m), 7.51-7.59 (1H, m), 7.70-7.76 (1H, m), 8.22 (0.5H, s), 8.28-8.36 (1.5H, s)

MS (ESI-): 539 (M-H)

Example 239

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(9-(fluorenylmethoxycarbonylamino)acetyl amino)phenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (478 mg) was dissolved in a solution of 20% piperidine in N,N-dimethylformamide (8 ml) at room temperature. After being stirred at the same temperature for 1 hour, the reaction mixture was concentrated in vacuo. The residue was purified by SiO₂ column chromatography (eluent: 1-5% MeOH in CHCl₃) to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(2-aminoacetyl amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (335 mg).

NMR (DMSO-d₆, δ): 1.37-1.65 (6H, m), 1.70-2.08 (4H, m),
2.34-2.50 (1H, m), 2.87-3.52 (8H, m), 3.72-3.90
(1H, m), 4.44, 4.75 (1H, s), 7.18-7.25 (1H, m),
7.32-7.44 (3H, m), 7.52-7.60 (1H, m), 8.02 (1H, s)

5 MS (ESI+): 522 (M+H)

Example 240

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(3-aminopropionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-
10 2H-thiopyran-2-acetamide 1,1-dioxide (1.56 g) was obtained in a similar manner to that of Example 239.

NMR (DMSO-d₆, δ): 1.32-2.09 (10H, m), 2.32-2.48 (3H, m),
2.72-3.56 (8H, m), 3.72-3.90 (1H, m), 4.45, 4.75
(1H, s), 7.17-7.24 (1H, m), 7.28-7.51 (3H, m),
15 7.43-7.54 (1H, m), 8.01 (1H, s), 12.4 (1H, br s)

MS (ESI-): 534 (M-H)

Example 241

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(methoxycarbonylamino)acetyl amino)phenyl)-2-thienyl]-
20 3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (88 mg) was obtained in a similar manner to that of Example 130.

NMR (CDCl₃, δ): 1.36-1.72 (8H, m), 1.87-1.99 (2H, m), 2.07-2.27 (2H, m), 2.79-2.92 (2H, m), 3.00-
25 3.23 (2H, m), 3.28-3.52 (1H, m), 3.68-3.76 (1H, m), 3.75 (3H, s), 3.96-4.12 (2H, m), 4.53, 4.84 (1H, s), 5.76-5.88 (1H, m), 7.05-7.22 (5H, m), 7.36-7.55 (2H, m), 8.40 (1H, s)

MS (ESI-): 578 (M-H)

30

Example 242

To a solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-formylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg) in tetrahydrofuran (1.5 ml)
35 was added dropwise sodium borohydride (8.71 mg) in water

(0.7 ml) at room temperature. After being stirred for 30 minutes, the reaction is stopped by adding 1% aqueous citric acid solution. The reaction mixture is extracted with ethyl acetate and the solution was washed with brine, dried over
5 MgSO_4 and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: 0.5-3% methanol in chloroform) to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-hydroxymethylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (96 mg) as an amorphous solid.
10

NMR (CDCl_3 , δ): 1.38-1.72 (6H, m), 1.81-2.00 (2H, m),
2.03-2.25 (2H, m), 2.67-3.17 (6H, m), 3.29-3.51
(1H, m), 3.61-3.72 (1H, m), 4.52, 4.81 (1H, s),
4.72 (2H, d, $J=6.0\text{Hz}$), 7.25-7.41 (4H, m), 7.52 (1H,
15 d, $J=8.5\text{Hz}$), 7.60 (1H, s)
MS (ESI-): 478 (M-H)

Example 243

A solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-ethenylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg), microencapsulated osmium
20 tetraoxide (5.34 mg) and N-methylmorpholine N-oxide (98.5 mg) in a mixture of H_2O -acetone-acetonitrile (1:1:1) (3.0 ml) was stirred at room temperature for 12 hours. After the
25 reaction was completed, the catalyst was separated by filtration. After washing with methanol, combined filtrates were concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: 0.5-3% methanol in chloroform) to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-(cis-1,2-dihydroxyethyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide as an amorphous solid (200
30 mg).

NMR (CDCl_3 , δ): 1.38-1.75 (6H, m), 1.90-2.00 (2H, m),
35 2.07-2.23 (2H, m), 2.60-2.89 (2H, m), 3.09-3.17

(4H, m), 3.25-3.50 (1H, m), 3.59-3.71 (1H, m),
3.73-3.82 (1H, m), 4.52, 4.80 (1H, s), 4.80-4.88
(1H, m), 7.34-7.40 (3H, m), 7.54-7.59 (3H, m)

MS (ESI-): 508 (M-H)

5

Example 244

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
(phenoxy carbonyloxymethyl)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (620 mg) was
10 obtained from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-
hydroxymethylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (500 mg) in a similar
manner to that of Example 130.

NMR (CDCl₃, δ): 1.38-1.75 (6H, m), 1.90-2.01 (2H, m),
15 2.06-2.23 (2H, m), 2.65-2.90 (2H, m), 3.04-3.17
(4H, m), 3.30-3.50 (1H, m), 3.62-3.70 (1H, m),
4.53, 4.81 (1H, s), 5.28 (2H, s), 7.19 (2H, d,
J=8.5Hz), 7.25-7.31 (4H, m), 7.37-7.42 (4H, m),
7.59-7.61 (1H, m), 7.66 (1H, s)

20 MS (ESI-): 598 (M-H)

Example 245

To a solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-
(3-(phenoxy carbonyloxymethyl)phenyl)-2-thienyl]-3,4,5,6-
25 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg) in
N,N-dimethylformamide (3 ml) was added 40% aqueous
methylamine (0.17 ml). After being stirred for 3 hours at
the same temperature, the mixture was concentrated in vacuo.
The residue was diluted with ethyl acetate, washed with 1%
30 aqueous citric acid solution, sat. NaHCO₃ solution and brine,
dried over MgSO₄ and concentrated in vacuo. The resulting
residue was purified by silica gel column chromatography
(eluent: CHCl₃) to give (2S)-N-(2-tetrahydropyranyloxy)-2-
[5-(3-(methylaminocarbonyloxy-
35 methyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-

acetamide 1,1-dioxide (150 mg) as an amorphous solid.

NMR (CDCl₃, δ): 1.37-1.75 (6H, m), 1.90-2.00 (2H, m),
2.05-2.23 (2H, m), 2.83 (3H, d, J=5.0Hz), 2.89-
3.17 (6H, m), 3.29-3.50 (1H, m), 3.61-3.71 (1H, m),
4.53, 4.81 (1H, s), 5.11 (2H, s), 7.25-7.31 (2H,
m), 7.36 (1H, dd, J=8.0, 8.0Hz), 7.51-7.59 (3H, m)
MS (ESI-): 535 (M-H)

Example 246

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-(methylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (270 mg) was obtained from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-(2-carboxyethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (300 mg) in a similar manner to that of Example 32.

NMR (CDCl₃, δ): 1.38-1.73 (6H, m), 1.88-2.02 (2H, m),
2.09-2.25 (2H, m), 2.78-2.89 (2H, m), 2.96 (3H, d, J=5Hz), 3.05-3.19 (4H, m), 3.29-3.51 (1H, m),
3.65-3.75 (1H, m), 4.54, 4.84 (1H, s), 6.40 (1H, d, J=15Hz), 7.20-7.59 (7H, m), 8.78 (1H, d, J=5Hz)

Example 247

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-(ethylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (280 mg) was obtained in a similar manner to that of Example 32.

NMR (DMSO-d₆, δ): 1.23 (3H, t, J=7.2Hz), 1.38-1.73 (6H, m), 1.90-2.01 (2H, m), 2.07-2.23 (2H, m), 2.78-2.88 (2H, m), 3.02-3.20 (4H, m), 3.38-3.48 (3H, m), 3.67-3.76 (1H, m), 4.54, 4.84 (1H, s), 6.41 (1H, d, J=15Hz), 7.21-7.59 (7H, m), 8.78 (1H, br)

Example 248

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-

(methylaminocarbonylmethoxy)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (720 mg) was obtained in a similar manner to that of Example 247.

5 NMR (DMSO-d₆, δ): 1.37-1.62 (6H, m), 1.67-1.81 (2H, m),
1.82-2.05 (2H, m), 2.33-2.45 (1H, m), 2.66 (3H, d,
J=4.5Hz), 2.90-3.50 (6H, m), 3.73-3.91 (1H, m),
4.45, 4.75 (1H, s), 4.50 (2H, s), 7.01 (2H, d,
J=9.0Hz), 7.16 (1H, d, J=4.0Hz), 7.32 (1H, d,
J=4.0Hz), 7.59 (2H, d, J=9.0Hz), 8.07 (1H, br),
10 11.23 (1H, s)

Example 249

A mixture of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-[3-(chloroacetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
15 thiopyran-2-acetamide 1,1-dioxide (98 mg),
n-tetrabutylammonium iodide (5 mg) and 2-aminoethanol (27.7 mg) in N,N-dimethylformamide (1.5 ml) was stirred for 14 hours at room temperature. The mixture was concentrated in vacuo and taken up between ethyl acetate and saturated
20 aqueous sodium bicarbonate. The separated organic layer was washed with brine, dried over sodium sulfate and evaporated in vacuo to give (2S)-N-(2-tetrahydropyranyloxy)-2-[5-[3-[(2-hydroxyethylamino)acetylaminophenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100
25 mg) as an amorphous solid.

NMR (CDCl₃, δ): 1.38-1.77 (6H, m), 1.89-2.00 (2H, m),
2.05-2.24 (2H, m), 2.68-2.91 (4H, m), 3.00-3.18
(4H, m), 3.29-3.52 (3H, m), 3.62-3.80 (3H, m),
4.53 (0.5H, s), 4.82 (0.5H, s), 7.22-7.32 (4H, m),
30 7.59-7.67 (1H, m), 7.69-7.75 (1H, m), 8.01 (1H, s),
9.48 (1H, s)

MS (ESI-): 564 (M-H)

Example 250

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[3-[(4-

morpholino)acetylaminophenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (96 mg) was obtained in a similar manner to that of Example 249.

5 NMR (CDCl₃, δ): 1.40-1.56 (4H, m), 1.61-1.73 (2H, m),
1.89-2.01 (2H, m), 2.06-2.32 (2H, m), 2.61-2.87
(6H, m), 3.05-3.19 (4H, m), 3.31-3.51 (1H, m),
3.62-3.74 (1H, m), 3.77-3.85 (4H, m), 4.53 (0.5H,
s), 4.81 (0.5H, s), 7.25-7.31 (2H, m), 7.33-7.38
10 (2H, m), 7.52-7.61 (1H, m), 7.74-7.80 (1H, m),
8.00-8.23 (1H, m), 9.10 (1H, s)
MS (ESI-): 590 (M-H)

The following compounds were obtained in a similar manner to that of Example 54.

15 Example 251

(2S)-N-Hydroxy-2-[5-(4-aminocarbonylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (40 mg)

20 NMR (DMSO-d₆, δ): 1.74-2.04 (4H, m), 2.37-2.46 (1H, m),
2.96-3.27 (4H, m), 3.4-3.54 (1H, m), 7.25 (1H, d,
J=4.0Hz), 7.48 (1H, br), 7.59 (1H, d, J=4.0Hz),
7.74 (2H, d, J=7.5Hz), 7.92 (2H, d, J=7.5Hz), 8.02
(1H, br), 8.85 (1H, br)
25 MS (ESI-): 407.1 (M-H)

Example 252

(2S)-N-Hydroxy-2-[5-(4-benzylaminocarbonyl)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (20 mg)

30 NMR (DMSO-d₆, δ): 1.74-2.08 (4H, m), 2.37-2.45 (1H, m),
2.95-3.26 (4H, m), 3.43-3.52 (1H, m), 4.49 (2H, d,
J=6.0Hz), 7.24 (2H, m), 7.31-7.34 (4H, m), 7.61
(1H, d, J=3.0Hz), 7.75 (2H, d, J=7.5Hz), 7.95 (2H,
35 d, J=7.5Hz), 8.84 (1H, s), 9.10 (1H, t, J=6.0Hz)

MS (ESI+): 523.1 (M+H+Na)

Example 253

(2S)-N-Hydroxy-2-[5-(3-(ethoxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (115 mg)

NMR (DMSO-d₆, δ): 1.28 (3H, t, J=7.0Hz), 1.73-2.05 (4H, m), 2.37-2.45 (1H, m), 2.96-3.25 (4H, m), 3.42-3.53 (1H, m), 4.15 (2H, q, J=7.0Hz), 7.20 (1H, d, J=4.0Hz), 7.28-7.34 (3H, m), 7.48 (1H, d, J=4.0Hz), 7.82 (1H, s), 8.84 (1H, br), 9.85 (1H, s), 10.60 (1H, br)

MS (ESI-): 451.2 (M-H)

Example 254

(2S)-N-Hydroxy-2-[5-(3-(benzylaminocarbonyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (50 mg)

NMR (DMSO-d₆, δ): 1.73-2.05 (4H, m), 2.36-2.47 (1H, m), 2.95-3.25 (4H, m), 3.41-3.52 (1H, m), 4.31 (2H, d, J=7.0Hz), 6.68 (1H, t, J=7.0Hz), 7.18-7.38 (10H, m), 7.86 (1H, s), 8.72 (1H, s), 8.84 (1H, s)

MS (ESI-): 512.3 (M-H)

Example 255

(2S)-N-Hydroxy-2-[5-(3-(n-propyloxycarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg)

NMR (DMSO-d₆, δ): 0.95 (3H, t, J=7.0Hz), 1.66 (2H, qt, J=7.0, 7.0Hz), 1.72-2.05 (4H, m), 2.35-2.46 (1H, m), 2.94-3.29 (4H, m), 3.40-3.53 (1H, m), 4.05 (2H, t, J=7.0Hz), 7.20 (1H, d, J=4.0Hz), 7.29-7.34 (3H, m), 7.38 (1H, d, J=4.0Hz), 7.83 (1H, s), 8.83 (1H, s), 9.73 (1H, s), 10.59 (1H, s)

MS (ESI-): 465.3 (M-H)

Example 256

(2S)-N-Hydroxy-2-[5-(3-(isopropoxycarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (90 mg)

NMR (DMSO-d₆, δ): 1.26 (6H, d, J=6.0Hz), 1.74-2.04 (4H, m), 2.35-2.55 (1H, m), 2.94-3.25 (4H, m), 3.40-3.51 (1H, m), 4.40 (1H, qq, J=6.0, 6.0Hz), 7.20 (1H, d, J=4.0Hz), 7.29-7.33 (3H, m), 7.36 (1H, d, J=4.0Hz), 7.85 (1H, s), 8.83 (1H, s), 9.67 (1H, s), 10.59 (1H, s)

MS (ESI-): 465.3 (M-H)

Example 257

(2S)-N-Hydroxy-2-[5-(3-(2-chloroethoxycarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

NMR (DMSO-d₆, δ): 1.75-2.05 (4H, m), 2.36-2.47 (1H, m), 2.94-3.29 (4H, m), 3.42-3.52 (1H, m), 3.88 (2H, d, J=6.0Hz), 4.35 (2H, d, J=6.0Hz), 7.21 (1H, d, J=4.0Hz), 7.32-7.36 (2H, m), 7.40 (1H, d, J=4.0Hz), 7.84 (1H, s), 8.83 (1H, s), 9.94 (1H, s), 10.08 (1H, s)

MS (ESI-): 485.2 (M-H)

Example 258

(2S)-N-Hydroxy-2-[5-(3-valerylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (102 mg)

NMR (DMSO-d₆, δ): 0.91 (3H, t, J=8Hz), 1.24-1.41 (2H, m), 1.52-1.66 (2H, m), 1.69-2.08 (4H, m), 2.33 (2H, t, J=8Hz), 2.32-2.48 (1H, m), 2.92-3.28 (4H, m), 3.37-3.54 (1H, m), 7.20 (1H, d, J=3Hz), 7.34 (2H, d, J=3Hz), 7.40 (1H, d, J=3Hz), 7.42-7.52 (1H, m), 7.99 (1H, s), 10.00 (1H, s), 10.60 (1H, s)

MS (ESI-): 463 (M-H)

Example 259

(2S)-N-Hydroxy-2-[5-(3-(ethylthiocarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (92 mg)

NMR (DMSO-d₆, δ): 1.26 (3H, t, J=8Hz), 1.72-2.08 (4H, m), 2.36-2.49 (1H, m), 2.89 (2H, q, J=8Hz), 2.94-3.30 (4H, m), 3.39-3.55 (1H, m), 7.21 (1H, d, J=3Hz), 7.32-7.44 (4H, m), 7.90 (1H, s), 8.85 (1H, s), 10.39 (1H, s), 10.60 (1H, s)

MS (ESI+): 469 (M+H)

Example 260

(2S)-N-Hydroxy-2-[5-(3-(methylthiocarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (130 mg)

NMR (DMSO-d₆, δ): 1.68-2.08 (4H, m), 2.33 (3H, s), 2.35-2.46 (1H, m), 2.92-3.38 (4H, m), 3.39-3.53 (1H, m), 7.21 (1H, d, J=3Hz), 7.29-7.46 (4H, m), 7.90 (1H, s)

MS (ESI-): 453 (M-H)

Example 261

(2S)-N-Hydroxy-2-[5-(3-(benzyloxycarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (60.2 mg)

NMR (DMSO-d₆, δ): 1.68-2.07 (4H, m), 2.32-2.48 (1H, m), 2.92-3.34 (4H, m), 3.52-3.65 (1H, m), 5.18 (2H, s), 7.21 (1H, d, J=3Hz), 7.26-7.50 (10H, m), 7.85 (1H, s), 9.91 (1H, s), 10.60 (1H, s)

MS (ESI-): 513 (M-H)

Example 262

(2S)-N-Hydroxy-2-[5-(3-(2-(t-butoxycarbonylamino)-

acetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (40 mg)

NMR (DMSO-d₆, δ): 1.40 (9H, s), 1.66-2.08 (4H, m), 2.35-2.48 (1H, m), 2.92-3.32 (4H, m), 3.45-3.53 (1H, m), 3.73 (2H, d, J=7Hz), 7.07 (1H, t, J=7Hz), 7.22 (1H, d, J=3Hz), 7.32-7.54 (4H, m), 7.97 (1H, s), 10.05 (1H, s), 10.61 (4H, s)

MS (ESI-): 536 (M-H)

10 Example 263

(2S)-N-Hydroxy-2-[5-(3-(2-(4-chlorophenoxy)-acetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (90 mg)

NMR (DMSO-d₆, δ): 1.71-2.09 (4H, m), 2.35-2.49 (1H, m), 2.94-3.29 (4H, m), 3.42-3.55 (1H, m), 4.74 (2H, s), 7.00-7.12 (2H, m), 7.22 (1H, br s), 7.32-7.47 (5H, m), 7.51-7.62 (1H, m), 8.02 (1H, s), 8.84 (1H, s), 10.22 (1H, s), 10.60 (1H, s)

MS (ESI-): 547 (M-H)

20 Example 264

(2S)-N-Hydroxy-2-[5-(3-(phenoxycarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (88 mg)

NMR (DMSO-d₆, δ): 1.68-2.09 (4H, m), 2.32-2.48 (1H, m), 2.92-3.30 (4H, m), 3.56-3.72 (1H, m), 7.17-7.30 (4H, m), 7.31-7.51 (6H, m), 7.89 (1H, s), 10.37 (1H, s), 10.61 (1H, s)

MS (ESI-): 499 (M-H)

30 Example 265

(2S)-N-Hydroxy-2-[5-(3-(2-(4-chlorophenyl)acetylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (95 mg)

NMR (DMSO-d₆, δ): 1.68-2.09 (4H, m), 2.35-2.48 (1H, m),

2.92-3.32 (4H, m), 3.54-3.66 (1H, m), 3.68 (2H, s),
7.20 (1H, d, J=3Hz), 7.28-7.52 (8H, m), 7.99 (1H,
s), 10.33 (1H, s), 10.60 (1H, s)

MS (ESI-): 531 (M-H)

5

Example 266

(2S)-N-Hydroxy-2-[5-(3-(2-(4-morpholinocarbonylamino)-
acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (50 mg)

10 NMR (DMSO-d₆, δ): 1.71-2.08 (4H, m), 2.36-2.48 (1H, m),
2.94-3.62 (13H, m), 3.82 (2H, d, J=7Hz), 6.96 (1H,
t, J=7Hz), 7.21 (1H, d, J=3Hz), 7.31-7.49 (4H, m),
8.02 (1H, s), 8.84 (1H, br s)

MS (ESI-): 549 (M-H)

15

Example 267

(2S)-N-Hydroxy-2-[5-(3-(2-(N-ethyl-N-methylamino-
carbonyloxy)acetylaminophenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (133 mg)

20 NMR (DMSO-d₆, δ): 1.05, 1.12 (3H, t, J=8Hz), 1.68-2.07
(4H, m), 2.35-2.48 (1H, m), 2.76-3.36 (9H, m),
3.39-3.54 (1H, m), 4.63 (2H, s), 7.21 (1H, d,
J=3Hz), 7.32-7.47 (4H, m), 8.00 (1H, s), 8.85 (1H,
s), 10.18 (1H, s), 10.61 (1H, s)

25 MS (ESI-): 522 (M-H)

Example 268

(2S)-N-Hydroxy-2-[5-(3-(isopropoxyacetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
30 acetamide 1,1-dioxide (204 mg)

NMR (DMSO-d₆, δ): 1.78 (6H, d, J=8Hz), 1.72-2.08 (4H,
m), 2.35-2.49 (1H, m), 2.94-3.31 (4H, m), 3.42-
3.56 (1H, m), 3.63-3.77 (1H, m), 4.04 (2H, s),
7.22 (1H, d, J=3Hz), 7.32-7.43 (2H, m), 7.40 (1H,
35 d, J=3Hz), 7.56-7.64 (1H, m), 8.02 (1H, s), 8.85

(1H, s), 9.68 (1H, s), 10.60 (1H, s)

MS (ESI+): 482 (M+H)

Example 269

5 (2S)-N-Hydroxy-2-[5-(3-(2-(2-oxo-1,3-oxazolidinyl-3-yl)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (480 mg)

NMR (DMSO-d₆, δ): 1.65-2.09 (4H, m), 2.32-2.51 (1H, m),
2.88-3.53 (5H, m), 3.66 (2H, t, J=8Hz), 4.04 (2H,
10 s), 4.34 (2H, t, J=8Hz), 7.21 (1H, d, J=3Hz),
7.30-7.51 (4H, m), 8.03 (1H, s), 10.37 (1H, s),
10.62 (1H, s)

MS (ESI-): 506 (M-H)

15 Example 270

(2S)-N-Hydroxy-2-[5-(3-(4-methoxyphenylaminocarbonyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (140 mg)

NMR (DMSO-d₆, δ): 1.73-2.04 (4H, m), 2.38-2.45 (1H, m),
20 2.95-3.26 (4H, m), 3.39-3.54 (1H, m), 3.72 (3H, s),
6.86 (2H, d, J=7.5Hz), 7.20 (1H, d, J=4.0Hz),
7.23-7.32 (3H, m), 7.37 (2H, d, J=7.5Hz), 7.50 (1H,
d, J=4.0Hz), 7.87 (1H, s), 8.50 (1H, s), 8.72 (1H,
s), 8.84 (1H, s), 10.59 (1H, s)

25 MS (ESI-): 528.3 (M-H)

Example 271

(2S)-N-Hydroxy-2-[5-(3-(3-pyridylaminocarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

NMR (DMSO-d₆, δ): 1.75-2.05 (4H, m), 2.37-2.48 (1H, m),
2.96-3.25 (4H, m), 3.58-3.69 (1H, m), 7.21 (1H, d,
J=4.0Hz), 7.30-7.36 (3H, m), 7.42 (1H, d, J=4.0Hz),
7.82 (1H, dd, J=7.5, 5.0Hz), 7.90 (1H, s), 8.29
35 (12H, d, J=7.5Hz), 8.45 (1H, d, J=5.0Hz), 9.03 (1H,

s), 9.48 (1H, s), 9.85 (1H, s), 10.60 (1H, s)
MS (ESI-): 499.2 (M-H)

Example 272

5 (2S)-N-Hydroxy-2-[5-{3-(((2S)-2-aminopropionyl)amino)-phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (120 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-{3-(((2S)-2-tert-butoxycarbonylamino)propionyl)amino)phenyl}-2-thienyl]-
10 3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide
NMR (DMSO-d₆, δ): 1.50 (3H, d, J=7.0Hz), 1.72-2.03 (4H, m), 2.35-2.46 (1H, m), 2.95-3.27 (4H, m), 3.43-3.54 (1H, m), 4.05 (1H, br t, J=7.0Hz), 7.21 (1H, d, J=4.0Hz), 7.37-7.43 (3H, m), 7.55 (1H, d, J=7.5Hz),
15 7.95 (1H, s), 8.28-8.32 (3H, m), 10.63 (1H, s), 10.81 (1H, s)
MS (ESI-): 450.7 (M-H)

Example 273

20 (2S)-N-Hydroxy-2-[5-{3-(((2R)-2-(tert-butoxycarbonyl-amino)propionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (30 mg)
NMR (DMSO-d₆, δ): 1.27 (3H, d, J=6.0Hz), 1.38 (9H, s), 1.74-2.04 (4H, m), 2.37-2.42 (1H, m), 2.95-3.25 (4H, m), 3.38-3.51 (1H, m), 4.08-4.15 (1H, m),
25 7.10 (1H, d, J=7.0Hz), 7.20 (1H, d, J=4.0Hz), 7.31-7.36 (2H, m), 7.40 (1H, d, J=4.0Hz), 7.50 (1H, br), 7.96 (1H, s), 8.83 (1H, s), 10.04 (1H, s), 10.60 (1H, s)
30 MS (ESI-): 550.3 (M-H)

Example 274

(2S)-N-Hydroxy-2-[5-{3-(((2R)-2-aminopropionyl)amino)-phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (130 mg) from (2S)-N-(2-

tetrahydropyranyloxy)-2-[5-{3-(((2R)-2-tert-butoxycarbonylamino)propionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

5 NMR (DMSO-d₆, δ): 1.50 (3H, d, J=7.0Hz), 1.72-2.03 (4H, m), 2.35-2.46 (1H, m), 2.95-3.27 (4H, m), 3.43-3.54 (1H, m), 4.05 (1H, br t, J=7.0Hz), 7.21 (1H, d, J=4.0Hz), 7.37-7.43 (3H, m), 7.55 (1H, d, J=7.5Hz), 7.95 (1H, s), 8.28-8.32 (3H, m), 10.63 (1H, s), 10.81 (1H, s)

10 MS (ESI-): 452.1 (M-H)

Example 275

(2S)-N-Hydroxy-2-[5-{3-(2-(4-methylphenoxy)-acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

15 NMR (DMSO-d₆, δ): 1.74-2.04 (4H, m), 2.24 (3H, s), 2.37-2.45 (1H, m), 2.95-3.26 (4H, m), 3.44-3.53 (1H, m), 4.67 (2H, s), 6.90 (2H, d, J=7.5Hz), 7.11 (2H, d, J=7.5Hz), 7.21 (1H, d, J=4.0Hz), 7.34-7.37 (2H, m), 20 7.42 (1H, d, J=4.0Hz), 7.56 (1H, d, J=6.0Hz), 8.01 (1H, s), 8.82 (1H, s), 10.17 (1H, s), 10.59 (1H, s)

MS (ESI-): 528.1 (M-H)

25 Example 276

(2S)-N-Hydroxy-2-[5-{3-(2-N,N-dimethylamino)-acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (65 mg)

30 NMR (DMSO-d₆, δ): 1.74-2.05 (4H, m), 2.36-2.45 (1H, m), 2.89 (6H, s), 2.96-3.27 (4H, m), 3.44-3.54 (1H, m), 4.17 (2H, s), 7.22 (1H, d, J=4.0Hz), 7.38-7.42 (2H, m), 7.50 (1H, d, J=5.0Hz), 7.95 (1H, s), 8.84 (1H, br), 9.88 (1H, br), 10.60 (1H, s), 10.82 (1H, s)

MS (ESI-): 464.3 (M-H)

Example 277

(2S)-N-Hydroxy-2-[5-(3-(allyloxycarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (50 mg)

5 NMR (DMSO-d₆, δ): 1.73-2.04 (4H, m), 2.36-2.45 (1H, m),
2.95-3.25 (4H, m), 3.41-3.49 (1H, m), 4.63 (2H, d,
J=5.0Hz), 5.25 (1H, d, J=8.0Hz), 5.38 (1H, d,
J=8.0Hz), 5.93-6.06 (1H, m), 7.20 (1H, d, J=4.0Hz),
7.30-7.35 (3H, m), 7.49 (1H, d, J=4.0Hz), 7.84 (1H,
10 s), 8.83 (1H, s), 9.85 (1H, s)
MS (ESI-): 463.3 (M-H)

Example 278

15 (2S)-N-Hydroxy-2-[5-(3-ethoxycarbonylmethylamino-carbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (40 mg)

NMR (DMSO-d₆, δ): 1.23 (3H, t, J=7.5Hz), 1.73-2.05 (4H,
m), 2.36-2.47 (1H, m), 2.94-3.25 (4H, m), 3.42-
3.54 (1H, m), 3.87 (2H, d, J=7.0Hz), 4.13 (2H, q,
20 J=7.5Hz), 6.50 (1H, t, J=7.0Hz), 7.18 (1H, d,
J=4.0Hz), 7.21-7.30 (3H, m), 7.37 (1H, d, J=4.0Hz),
7.83 (1H, s), 8.83 (1H, s), 8.96 (1H, s)
MS (ESI-): 508.3 (M-H)

Example 279

25 (2S)-N-Hydroxy-2-[5-(3-(benzyloxyacetylaminophenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (55 mg)

NMR (DMSO-d₆, δ): 1.75-2.06 (4H, m), 2.36-2.46 (1H, m),
30 2.95-3.25 (4H, m), 3.42-3.53 (1H, m), 4.11 (2H, s),
4.64 (2H, s), 7.21 (1H, d, J=4.0Hz), 7.28-7.43 (8H,
m), 7.54-7.57 (1H, m), 8.01 (1H, s), 8.82 (1H, s),
9.90 (1H, s), 10.60 (1H, s)
MS (ESI-): 527.3 (M-H)

Example 280

(2S)-N-Hydroxy-2-[5-(3-(cyclopentylcarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg)

- 5 NMR (DMSO-d₆, δ): 1.52-2.06 (12H, m), 2.36-2.47 (1H, m),
2.78 (1H, tt, J=7.0, 7.0Hz), 2.95-3.25 (4H, m),
3.40-3.54 (1H, m), 7.20 (1H, d, J=4.0Hz), 7.32-
7.34 (2H, m), 7.40 (1H, d, J=4.0Hz), 7.45-7.49 (1H,
m), 8.03 (1H, s), 8.84 (1H, s), 9.98 (1H, s),
10 10.61 (1H, s)
MS (ESI-): 475.3 (M-H)

Example 281

- 15 (2S)-N-Hydroxy-2-[5-(3-((2-hydroxyethyl)-aminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (20 mg)

- NMR (DMSO-d₆, δ): 1.72-2.04 (4H, m), 2.40-2.45 (1H, m),
2.93-3.25 (6H, m), 3.41-3.50 (3H, m), 4.75 (1H, t,
J=5.0Hz), 6.22 (1H, t, J=5.0Hz), 7.16-7.25 (3H, m),
20 7.35 (1H, d, J=4.0Hz), 7.82 (1H, s), 8.71 (1H, s),
8.83 (1H, s)
MS (ESI-): 466.4 (M-H)

Example 282

- 25 (2S)-N-Hydroxy-2-[5-(3-((2-aminoethoxy)carbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (20 mg)

- NMR (DMSO-d₆, δ): 1.74-2.07 (4H, m), 2.35-2.44 (1H, m),
2.95-3.27 (4H, m), 3.48-3.66 (5H, m), 7.12-7.51
30 (4H, m), 7.86-7.90 (2H, m), 8.00-8.08 (2H, m),
9.10 (1H, s), 9.85 (1H, s), 10.62 (1H, s)
MS (ESI+): 468.3 (M+H)

Example 283

- 35 (2S)-N-Hydroxy-2-[5-(3-(3-chloropropionylamino)phenyl)-

2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (95 mg)

5 NMR (DMSO-d₆, δ): 1.73-2.06 (4H, m), 2.37-2.46 (1H, m),
2.84 (2H, t, J=6.0Hz), 2.95-3.26 (4H, m), 3.43-
3.56 (1H, m), 3.90 (2H, t, J=6.0Hz), 7.21 (1H, d,
J=4.0Hz), 7.35-7.40 (2H, m), 7.42 (1H, d, J=4.0Hz),
7.47-7.52 (1H, m), 8.00 (1H, s), 8.85 (1H, s)

MS (ESI-): 469.1 (M-H)

10 Example 284

(2S)-N-Hydroxy-2-[5-(4-(methanesulfonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (40 mg)

15 NMR (DMSO-d₆, δ): 1.72-2.05 (4H, m), 2.34-2.44 (1H, m),
2.89 (3H, s), 2.93-3.23 (4H, m), 3.41-3.51 (1H, m),
7.12 (2H, d, J=7.5Hz), 7.15 (1H, d, J=4.0Hz), 7.31
(1H, d, J=4.0Hz), 7.50 (2H, d, J=7.5Hz)

MS (ESI-): 457.3 (M-H)

20 Example 285

(2S)-N-Hydroxy-2-[5-(4-(2-(phenylaminocarbonyl)-ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (40 mg)

25 NMR (DMSO-d₆, δ): 1.73-2.07 (4H, m), 2.38-2.48 (1H, m),
2.97-3.54 (5H, m), 6.86 (1H, d, J=16Hz), 7.06 (1H,
dd, J=8.0, 8.0Hz), 7.24 (1H, d, J=4.0Hz), 7.34 (2H,
dd, J=8.0, 8.0Hz), 7.56 (1H, d, J=4.0Hz), 7.61 (1H,
d, J=16Hz), 7.65-7.75 (6H, m), 8.85 (1H, s), 10.2
(1H, s), 10.6 (1H, s)

30

Example 286

(2S)-N-Hydroxy-2-[5-(4-(2-(4-methoxyphenylamino)-carbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

35 NMR (DMSO-d₆, δ): 1.72-2.07 (4H, m), 2.37-2.46 (1H, m),

2.97-3.52 (5H, m), 3.74 (3H, s), 6.83 (1H, d, J=16Hz), 6.92 (2H, d, J=8.5Hz), 7.24 (1H, d, J=4.0Hz), 7.54-7.75 (8H, m), 8.85 (1H, s), 10.08 (1H, s), 10.6 (1H, s)

5

Example 287

(2S)-N-Hydroxy-2-[5-(4-(2-(4-fluorophenylamino-carbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80 mg)

10 NMR (DMSO-d₆, δ): 1.73-2.07 (4H, m), 2.37-2.46 (1H, m), 2.98-3.53 (5H, m), 6.83 (1H, d, J=16Hz), 7.18 (2H, dd, J=8.5, 8.5Hz), 7.24 (1H, d, J=4.0Hz), 7.57-7.75 (8H, m), 8.85 (1H, s), 10.3 (1H, s), 10.6 (1H, s)

15

Example 288

(2S)-N-Hydroxy-2-[5-(4-(ethylcarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

20 NMR (DMSO-d₆, δ): 1.13 (3H, dd, J=7.5, 7.5Hz), 1.71-2.07 (4H, m), 2.36-2.46 (1H, m), 2.62 (2H, ddd, J=7.5, 7.5, 7.5Hz), 2.96-3.52 (5H, m), 7.20-7.21 (3H, m), 7.46 (1H, d, J=4.0Hz), 7.68 (2H, d, J=8.5Hz), 8.85 (1H, s)

25 MS (ESI-): 436 (M-H)

Example 289

(2S)-N-Hydroxy-2-[5-(4-(methoxycarbonylaminomethyl)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (45 mg)

30 NMR (DMSO-d₆, δ): 1.70-2.06 (4H, m), 2.35-2.45 (1H, m), 2.96-3.50 (5H, m), 3.56 (3H, s), 4.19 (2H, d, J=7.0Hz), 7.20 (1H, d, J=4.0Hz), 7.29 (2H, d, J=8.5Hz), 7.43 (1H, d, J=4.0Hz), 7.60 (2H, d, J=8.5Hz), 7.70 (1H, t, J=7.0Hz), 8.85 (1H, s),

35

10.60 (1H, s)

MS (ESI-): 451 (M-H)

Example 290

5 (2S)-N-Hydroxy-2-[5-(4-(ethylcarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg)

NMR (DMSO-d₆, δ): 0.98 (3H, t, J=7.2Hz), 1.70-2.07 (4H, m), 2.33-2.45 (1H, m), 2.54 (2H, q, J=7.2Hz),
10 2.95-3.50 (5H, m), 4.86 (2H, s), 6.95 (2H, d, J=8.5Hz), 7.16 (1H, d, J=4.0Hz), 7.34 (1H, d, J=4.0Hz), 7.55 (2H, d, J=8.5Hz), 8.84 (1H, br)

MS (ESI-): 450 (M-H)

15 Example 291

(2S)-N-Hydroxy-2-[5-(4-(cyclopropylaminocarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

NMR (DMSO-d₆, δ): 0.46-0.51 (2H, m), 0.60-0.66 (2H, m),
20 1.70-2.07 (4H, m), 2.34-2.45 (1H, m), 2.66-2.75 (1H, m), 2.95-3.50 (5H, m), 4.47 (2H, s), 6.99 (2H, d, J=8.5Hz), 7.16 (1H, d, J=4.0Hz), 7.35 (1H, d, J=4.0Hz), 7.57 (2H, d, J=8.5Hz), 8.15 (1H, br), 8.84 (1H, s), 10.59 (1H, s)

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Example 292

(2S)-N-Hydroxy-2-[5-(4-(n-propylaminocarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

30 NMR (DMSO-d₆, δ): 0.82 (3H, t, J=7.5Hz), 1.39-1.50 (2H, m), 1.73-2.07 (4H, m), 2.35-2.45 (1H, m), 2.95-3.52 (7H, m), 4.50 (2H, s), 7.01 (2H, d, J=8.5Hz), 7.17 (1H, d, J=4.0Hz), 7.35 (1H, d, J=4.0Hz), 7.58 (2H, d, J=8.5Hz), 8.11 (1H, br), 8.85 (1H, s),
35 10.59 (1H, s)

MS (ESI-): 479 (M-H)

Example 293

(2S)-N-Hydroxy-2-[5-(3-hydroxyphenyl)-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120
mg)

NMR (DMSO-d₆, δ): 1.70-2.05 (4H, m), 2.36-2.45 (1H, m),
2.95-3.50 (5H, m), 6.71-6.74 (1H, m), 7.00 (1H, s),
7.06 (1H, d, J=8.0Hz), 7.17-7.25 (2H, m), 7.39 (1H,
d, J=4.0Hz), 8.85 (1H, s), 9.62 (1H, s), 10.60 (1H,
s)

MS (ESI-): 380 (M-H)

Example 294

(2S)-N-Hydroxy-2-[5-(3-butylaminocarbonylamino)phenyl]-
2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (170 mg)

NMR (DMSO-d₆, δ): 0.90 (3H, dd, J=7.2, 7.2Hz), 1.27-1.37
(2H, m), 1.37-1.47 (2H, m), 1.70-2.05 (4H, m),
2.37-2.45 (1H, m), 2.95-3.50 (7H, m), 6.16 (1H, dd,
J=7.0, 7.0Hz), 7.17-7.28 (4H, m), 7.37 (1H, d,
J=4.0Hz), 7.84 (1H, s), 8.55 (1H, s), 10.6 (1H, s)

MS (ESI-): 478 (M-H)

Example 295

(2S)-N-Hydroxy-2-[5-(3-(1-naphtyl)aminocarbonylamino)-
phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (250 mg)

NMR (DMSO-d₆, δ): 1.72-2.07 (4H, m), 2.38-2.47 (1H, m),
2.95-3.31 (5H, m), 7.22 (1H, d, J=4.0Hz), 7.29-
7.37 (3H, m), 7.44 (1H, d, J=4.0Hz), 7.47-7.68 (4H,
m), 7.94-7.96 (2H, m), 8.02 (1H, d, J=8.3Hz), 8.15
(1H, d, J=8.3Hz), 8.85 (1H, s), 9.27 (1H, s), 10.6
(1H, s)

MS (ESI-): 548 (M-H)

Example 296

(2S)-N-Hydroxy-2-[5-(3-(allylamino)carbonylamino)-phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)

NMR (DMSO-d₆, δ): 1.70-2.07 (4H, m), 2.36-2.45 (1H, m), 2.96-3.25 (5H, m), 3.72-3.76 (2H, m), 5.02-5.19 (2H, m), 5.80-5.94 (1H, m), 6.29-6.32 (1H, m), 7.18-7.26 (4H, m), 7.38 (1H, d, J=4.0Hz), 7.84 (1H, s), 8.68 (1H, s), 10.6 (1H, s)

MS (ESI-): 462 (M-H)

Example 297

(2S)-N-Hydroxy-2-[5-(3-(isobutylaminocarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (170 mg)

NMR (DMSO-d₆, δ): 0.88 (6H, d, J=6.6Hz), 1.65-2.07 (5H, m), 2.40-2.47 (1H, m), 2.94 (2H, dd, J=6.5, 6.5Hz), 3.00-3.50 (5H, m), 6.23 (1H, dd, J=6.5, 6.5Hz), 7.17-7.20 (3H, m), 7.37 (1H, d, J=4.0Hz), 7.84 (1H, s), 8.54 (1H, s), 10.6 (1H, s)

MS (ESI-): 478 (M-H)

Example 298

(2S)-N-Hydroxy-2-[5-(3-(cyclohexylmethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg)

NMR (DMSO-d₆, δ): 0.83-0.95 (2H, m), 1.11-1.25 (3H, m), 1.60-1.75 (6H, m), 1.83-2.07 (4H, m), 2.37-2.45 (1H, m), 2.93-3.07 (4H, m), 3.08-3.30 (3H, m), 6.22 (1H, br), 7.19-7.28 (4H, m), 7.37 (1H, d, J=4.0Hz), 8.55 (1H, s), 10.6 (1H, s)

MS (ESI-): 518 (M-H)

35 Example 299

(2S)-N-Hydroxy-2-[5-(3-(2-methoxyethylaminocarbonyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

5 NMR (DMSO-d₆, δ): 1.71-2.06 (4H, m), 2.37-2.46 (1H, m),
2.95-3.01 (2H, m), 3.05-3.25 (3H, m), 3.28 (3H, s),
3.35-3.51 (4H, m), 6.21-6.25 (1H, m), 7.16-7.25
(4H, m), 7.37 (1H, d, J=4.0Hz), 7.83 (1H, s), 8.68
(1H, s), 8.79-8.86 (1H, br), 10.6 (1H, s)

MS (ESI-): 480 (M-H)

Example 300

(2S)-N-Hydroxy-2-[5-(3-(N-methyl-N-ethylaminocarbonyl)-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (55 mg)

15 NMR (DMSO-d₆, δ): 1.08 (3H, t, J=7.0Hz), 1.70-2.08 (4H,
m), 2.37-2.45 (1H, m), 2.94 (3H, s), 2.97-3.54 (7H,
m), 7.20 (1H, d, J=4.0Hz), 7.25 (2H, d, J=8.0Hz),
7.37 (1H, d, J=4.0Hz), 7.45 (2H, d, J=8.0Hz), 7.84
(1H, s), 8.84 (1H, s), 10.59 (1H, s)

20 MS (ESI-): 464 (M-H)

Example 301

(2S)-N-Hydroxy-2-[5-(4-(2-(N,N-dimethylaminocarbonyl)-ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (180 mg)

25 NMR (DMSO-d₆, δ): 1.70-2.08 (4H, m), 2.37-2.45 (1H, m),
2.93 (3H, s), 2.94-3.10 (2H, m), 3.17 (3H, s),
3.18-3.55 (3H, m), 7.20 (1H, d, J=4.0Hz), 7.25 (1H,
d, J=16Hz), 7.45 (1H, d, J=16Hz), 7.55 (1H, d,
30 J=4.0Hz), 7.66 (2H, d, J=8.5Hz), 7.75 (2H, d,
J=8.5Hz), 8.84 (1H, br), 10.60 (1H, s)

MS (ESI-): 461 (M-H)

Example 302

35 (2S)-N-Hydroxy-2-[5-(4-(2-(isopropylaminocarbonyl)-

ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg)

NMR (DMSO-d₆, δ): 1.11 (6H, d, J=6.5Hz), 1.70-2.07 (4H, m), 2.36-2.44 (1H, m), 2.97-3.55 (5H, m), 3.40-4.00 (1H, m), 6.62 (1H, d, J=16Hz), 7.23 (1H, d, J=4.0Hz), 7.40 (1H, d, J=16Hz), 7.55 (1H, d, J=4.0Hz), 7.58 (2H, d, J=8.5Hz), 7.69 (2H, d, J=8.5Hz), 7.99 (1H, d, J=7.5Hz), 10.6 (1H, s)

MS (ESI-): 475 (M-H)

Example 303

(2S)-N-Hydroxy-2-[5-(4-(2-(propylaminocarbonyl)-ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg)

NMR (DMSO-d₆, δ): 0.88 (3H, t, J=7.5Hz), 1.47 (2H, q, J=7.5Hz), 1.70-2.07 (4H, m), 2.35-2.45 (1H, m), 2.96-3.55 (7H, m), 6.65 (1H, d, J=16Hz), 7.23 (1H, d, J=4.0Hz), 7.40 (1H, d, J=16Hz), 7.55 (1H, d, J=4.0Hz), 7.60 (2H, d, J=8.5Hz), 7.69 (2H, d, J=8.5Hz), 8.10 (1H, t, J=7.0Hz), 10.6 (1H, s)

MS (ESI-): 475 (M-H)

Example 304

(2S)-N-Hydroxy-2-[5-(4-(methylaminocarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

NMR (DMSO-d₆, δ): 1.71-2.05 (4H, m), 2.35-2.45 (1H, m), 2.67 (3H, d, J=4.5Hz), 2.95-3.51 (5H, m), 7.15 (2H, d, J=8.7Hz), 7.21 (1H, d, J=4.0Hz), 7.43 (1H, d, J=4.0Hz), 7.63 (2H, d, J=8.7Hz), 7.65-7.68 (1H, m), 8.85 (1H, s), 10.6 (1H, s)

MS (ESI-): 437 (M-H)

Example 305

(2S)-N-Hydroxy-2-[5-(4-(ethylaminocarbonyloxy)phenyl)-

2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (130 mg)

5 NMR (DMSO- d_6 , δ): 1.08 (3H, dd, $J=7.2$, 7.2Hz), 1.71-2.05 (4H, m), 1.85-1.96 (1H, m), 2.95-3.30 (6H, m), 3.41-3.53 (1H, m), 7.15 (2H, d, $J=8.7$ Hz), 7.20 (1H, d, $J=4.0$ Hz), 7.43 (1H, d, $J=4.0$ Hz), 7.63 (2H, d, $J=8.7$ Hz), 7.80 (1H, dd, $J=7.0$, 7.0Hz), 8.85 (1H, s), 10.6 (1H, s)

10 MS (ESI-): 451 (M-H)

Example 306

(2S)-N-Hydroxy-2-[5-(5-acetyl-2-thienyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (20 mg)

15 NMR (DMSO- d_6 , δ): 1.68-2.07 (4H, m), 2.35-2.45 (1H, m), 2.53 (3H, s), 2.95-3.53 (5H, m), 7.21 (1H, d, $J=4.0$ Hz), 7.44 (1H, d, $J=4.0$ Hz), 7.51 (1H, d, $J=4.0$ Hz), 7.91 (1H, d, $J=4.0$ Hz), 8.85 (1H, s)

20 MS (ESI-): 412 (M-H)

The following compounds were obtained in a similar manner to that of Example 166.

Example 307

25 (2S)-N-Hydroxy-2-[5-(4-methoxyacetoxy)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

30 NMR (DMSO- d_6 , δ): 1.71-2.05 (4H, m), 2.36-2.45 (1H, m), 2.97-3.28 (4H, m), 3.41 (3H, s), 3.42-3.51 (1H, m), 4.36 (2H, s), 7.21 (1H, d, $J=4.0$ Hz), 7.22 (2H, d, $J=8.5$ Hz), 7.48 (1H, d, $J=4.0$ Hz), 7.70 (2H, d, $J=8.5$ Hz), 8.84 (1H, s)

MS (ESI-): 452 (M-H)

35 Example 308

(2S)-N-Hydroxy-2-[5-(4-(ethoxycarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80 mg)

5 NMR (DMSO-d₆, δ): 1.31 (3H, dd, J=7.5, 7.5Hz), 1.70-1.93 (4H, m), 2.36-2.47 (1H, m), 2.97-3.51 (5H, m), 4.27 (2H, ddd, J=7.5, 7.5, 7.5Hz), 7.21 (1H, d, J=4.0Hz), 7.30 (2H, d, J=8.5Hz), 7.49 (1H, d, J=4.0Hz), 7.69 (2H, d, J=8.5Hz)

10 MS (ESI-): 452 (M-H)

Example 309

(2S)-N-Hydroxy-2-[5-(4-(cyclopropylcarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

15 NMR (DMSO-d₆, δ): 1.03-1.06 (4H, m), 1.70-2.05 (5H, m), 2.36-2.47 (1H, m), 2.95-3.51 (5H, m), 7.17-7.21 (3H, m), 7.46 (1H, d, J=4.0Hz), 7.66 (2H, d, J=8.5Hz), 8.84 (1H, s), 10.58 (1H, s)

20 MS (ESI-): 448 (M-H)

Example 310

(2S)-N-Hydroxy-2-[5-(4-(ethoxycarbonylmethoxy)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

25 NMR (DMSO-d₆, δ): 1.22 (3H, t, J=7.2Hz), 1.70-2.07 (4H, m), 2.35-2.45 (1H, m), 2.95-3.52 (5H, m), 4.17 (2H, q, J=7.2Hz), 4.82 (2H, s), 6.97 (2H, d, J=8.5Hz), 7.16 (1H, d, J=4.0Hz), 7.34 (1H, d, J=4.0Hz), 7.56 (2H, d, J=8.5Hz), 8.83 (1H, s), 10.6 (1H, s)

30

Example 311

To a solution of 0.5M 4-chlorophenylisocyanate (192 mg) in dichloromethane (2.5 ml) was added N-[2-[2-(5-(3-aminophenyl)-2-thienyl)-1,1-dioxo-3,4,5,6-tetrahydro-2H-thiopyran-2-yl]acetyl]hydroxylamine trityl crowns (26 μmol,

35

13.2 $\mu\text{mol/crown} \times 2$). The reaction mixture was left overnight at ambient temperature. The crowns were washed with N,N-dimethylformamide, methanol and dichloromethane, successively. The crowns were treated with 5%

5 trifluoroacetic acid in dichloromethane for 1 hour at ambient temperature and removed from the solution. After the solution was evaporated under a stream of nitrogen, the residue was purified by reverse phase HPLC (0.1% trifluoroacetic acid in acetonitrile, 10-40% gradient) to
10 give (2S)-N-hydroxy-2-[5-(3-(4-chlorophenylaminocarbonyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (1.6 mg) as a white powder.

MS (ESI+): 551.3 (M+H+NH₃)

15 The following compounds were obtained in substantially the same manner as that of Example 311.

Example 312

(2S)-N-Hydroxy-2-[5-(3-(n-phenylaminocarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
20 acetamide 1,1-dioxide (1.2 mg)

MS (ESI-): 492.3 (M-H)

Example 313

25 (2S)-N-Hydroxy-2-[5-(3-(n-hexylaminocarbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.0 mg)

MS (ESI-): 506.4 (M-H)

Example 314

(2S)-N-Hydroxy-2-[5-(3-(3-chlorophenylaminocarbonyl-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (1.3 mg)

MS (ESI+): 550.7 (M+H+NH₃)

35

Example 315

(2S)-N-Hydroxy-2-[5-(3-((R)-2-amino-2-phenylacetyl)-amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (76 mg) was obtained in a similar manner to that of Example 54.

NMR (DMSO-d₆, δ): 1.64-2.11 (4H, m), 2.32-2.98 (1H, m), 2.87-3.62 (5H, m), 5.30 (1H, br s), 7.22 (1H, s), 7.34-7.82 (10H, m), 7.97 (1H, s), 8.91 (2H, br s), 10.66 (1H, br s), 11.27 (1H, s)

MS (ESI+): 514 (M+H)

Example 316

(2S)-N-Hydroxy-2-[5-(3-(3-(benzoylamino)-propionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (96 mg) was obtained in a similar manner to that of Example 199.

NMR (DMSO-d₆, δ): 1.64-2.10 (4H, m), 2.33-2.48 (1H, m), 2.58-2.76 (2H, m), 2.88-3.56 (9H, m), 7.21 (1H, br s), 7.30-7.64 (8H, m), 7.84 (2H, br s), 8.03 (1H, br s), 8.64 (1H, br s)

MS (ESI-): 554 (M-H)

Example 317

(2S)-N-Hydroxy-2-[5-(3-(3-(ethylaminocarbonylamino)-propionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (98 mg) was obtained in a similar manner to that of Example 199.

NMR (DMSO-d₆, δ): 0.96 (3H, t, J=7Hz), 1.69-2.10 (4H, m), 2.33-2.48 (1H, m), 2.90-3.64 (11H, m), 7.19 (1H, d, J=3Hz), 7.28-7.51 (5H, m), 8.04 (1H, s)

MS (ESI-): 521 (M-H)

Example 318

(2S)-N-Hydroxy-2-[5-(3-(3-(methanesulfonylamino)-propionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-

thiopyran-2-acetamide 1,1-dioxide (54 mg) was obtained in a similar manner to that of Example 199.

NMR (DMSO-d₆, δ): 1.22-2.12 (4H, m), 2.35-2.49 (1H, m),
2.58 (2H, t, J=7Hz), 2.99 (3H, s), 2.94-3.62 (7H,
5 m), 7.06-7.16 (1H, m), 7.22 (1H, d, J=3Hz), 7.33-
7.39 (2H, m), 7.40 (1H, d, J=3Hz), 7.43-7.52 (1H,
m), 8.01 (1H, s)

MS (ESI-): 528 (M-H)

10 Example 319

(2S)-N-Hydroxy-2-[5-(3-((4-piperidinyloxy)acetyl-amino)-
phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide hydrochloride (55 mg) was obtained
from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-((1-tert-
15 butoxycarbonyl-4-piperidinyloxy)acetyl-amino)phenyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide in a similar manner to that of Example 54.

NMR (DMSO-d₆, δ): 1.68-2.11 (8H, m), 2.34-2.98 (1H, m),
2.89-3.56 (8H, m), 3.66-3.80 (1H, m), 4.14 (2H, s),
20 7.11-7.62 (5H, m), 8.00 (1H, s), 8.85 (1H, s),
9.83 (1H, s), 10.60 (1H, s)

MS (ESI+): 522 (M+H)

The following compounds were obtained in a similar
25 manner to that of Example 89.

Example 320

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
(methanesulfonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-
30 2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

NMR (CDCl₃, δ): 1.32 (2H, br), 1.40-1.49 (2H, m),
1.64-1.68 (2H, m), 1.94 (2H, br), 2.10-2.20 (2H, m),
2.76-2.80 (2H, m), 3.00 (2H, s), 3.06-3.10 (2H, m),
3.15 (2H, br), 3.33-3.51 (1H, m), 3.65-3.74 (1H, m),
35 4.55 (1/2H, br), 4.82 (1/2H, br), 7.01 (1H, br),

7.11-7.16 (3H, m), 7.45 (2H, d, J=7.5Hz), 8.25
(1/2H, s), 8.33 (1/2H, s)

MS (ESI-): 541.4 (M-H)

5 Example 321

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(methoxycarbonylaminomethyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80 mg)

10 NMR (DMSO-d₆, δ): 1.37 (6H, m), 1.69-1.81 (2H, m),
1.82-2.07 (2H, m), 2.35-2.45 (1H, m), 2.90-3.50
(6H, m), 3.57 (3H, s), 3.72-3.88 (1H, m), 4.20 (2H,
d, J=7.0Hz), 4.45, 4.75 (1H, s), 7.20-7.22 (1H, m),
7.28 (2H, d, J=8.5Hz), 7.41-7.43 (1H, m), 7.61 (2H,
d, J=8.5Hz), 7.72 (1H, t, J=7.0Hz)

15 MS (ESI-): 535 (M-H)

Example 322

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(cyclopropylcarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

20 NMR (DMSO-d₆, δ): 1.03-1.07 (4H, m), 1.39-1.64 (6H, m),
1.70-2.05 (5H, m), 2.35-2.45 (1H, m), 2.90-3.51
(6H, m), 3.75-3.90 (1H, m), 4.45, 4.75 (1H, s),
7.02-7.05 (1H, m), 7.19 (2H, d, J=8.5Hz), 7.44-
25 7.47 (1H, m), 7.76 (2H, d, J=8.5Hz)

Example 323

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(ethoxycarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg)

30 NMR (DMSO-d₆, δ): 1.22 (3H, t, J=7.0Hz), 1.35-1.62 (6H,
m), 1.66-2.05 (4H, m), 2.35-2.45 (1H, m), 2.90-
3.50 (6H, m), 3.73-3.90 (1H, m), 4.18 (2H, q,
J=7.0Hz), 4.45, 4.75 (1H, s), 4.82 (2H, s), 6.98
35 (2H, d, J=8.5Hz), 7.16-7.21 (1H, m), 7.32-7.36 (1H,

m), 7.57 (2H, d, J=8.5Hz)

Example 324

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
5 (ethylcarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-
2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)

NMR (DMSO-d₆, δ): 0.98 (3H, t, J=7.2Hz), 1.35-1.65 (6H,
m), 1.67-2.05 (4H, m), 2.32-2.45 (1H, m), 2.54 (2H,
q, J=7.2Hz), 2.90-3.50 (6H, m), 3.74-3.89 (1H, m),
10 4.45, 4.75 (1H, s), 4.86 (2H, s), 6.95 (2H, d,
J=8.5Hz), 7.16-7.20 (1H, m), 7.31-7.35 (1H, m),
7.55 (2H, d, J=8.5Hz)

Example 325

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
15 (cyclopropylaminocarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (140 mg)

NMR (DMSO-d₆, δ): 0.45-0.50 (2H, m), 0.60-0.65 (2H, m),
1.35-1.65 (6H, m), 1.70-2.07 (4H, m), 2.35-2.45
20 (1H, m), 2.65-2.74 (1H, m), 2.90-3.50 (6H, m),
3.75-3.90 (1H, m), 4.47 (2H, s), 4.45, 4.75 (1H,
s), 6.98 (2H, d, J=8.5Hz), 7.15-7.20 (1H, m),
7.30-7.35 (1H, m), 7.58 (2H, d, J=8.5Hz), 8.15 (1H,
br), 11.20 (1H, s)

25

Example 326

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-hydroxyphenyl)-
2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (205 mg)

NMR (DMSO-d₆, δ): 1.35-1.64 (6H, m), 1.66-2.05 (4H, m),
2.35-2.45 (1H, m), 2.90-3.50 (6H, m), 3.75-3.90
(1H, m), 4.45, 4.75 (1H, s), 6.70-6.73 (1H, m),
7.00-7.07 (2H, m), 7.16-7.21 (2H, m), 7.35-7.40
(1H, m), 9.61 (1H, s)

35

Example 327

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(5-acetyl-2-thienyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

5 NMR (CDCl₃, δ): 1.43-1.78 (6H, m), 1.85-1.98 (2H, m),
2.05-2.25 (2H, m), 2.58 (3H, s), 2.63-2.86 (2H, m),
2.95-3.17 (4H, m), 2.95-3.61 (1H, m), 3.65-3.82
(1H, m), 4.51, 4.83 (1H, s), 7.18 (1H, d, J=4.0Hz),
7.57 (1H, d, J=4.0Hz), 7.64 (1H, d, J=4.0Hz), 7.70
10 (1H, d, J=4.0Hz)

Example 328

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-aminocarbonylphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (49 mg) was obtained from
15 (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-carboxyphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (133 mg) in a similar manner to that of Example 32.

NMR (CDCl₃, δ): 1.45 (2H, br), 1.63-1.68 (2H, m), 1.94
20 (2H, br), 2.08-2.17 (2H, m), 2.30-2.36 (2H, m),
3.00-3.22 (4H, m), 3.26-3.47 (1H, m), 3.68-3.76
(1H, m), 4.55 (1/2H, br), 4.85 (1/2H, br), 7.43-
7.57 (5H, m), 7.63-7.70 (3H, m), 7.75-7.80 (1H, m)
MS (ESI+): 493.6 (M+H)

25

Example 329

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(benzylaminocarbonyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (85 mg) was obtained in
30 a similar manner to that of Example 328.

NMR (CDCl₃, δ): 1.51-1.60 (2H, m), 1.70-1.79 (4H, m),
1.89-1.96 (2H, m), 2.08-2.18 (2H, m), 2.76-2.83
(2H, br), 2.97-3.14 (4H, m), 3.40-3.64 (1H, m),
3.72-3.92 (1H, m), 4.60-4.65 (2H, m), 4.68 (1/2H,
35 br), 4.84 (1/2H, br), 7.20-7.37 (7H, m), 7.56-7.83

(4H, m)

MS (ESI-): 581.2 (M-H)

The following compounds were obtained in a similar
5 manner to that of Example 130.

Example 330

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
(ethoxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-
10 2H-thiopyran-2-acetamide 1,1-dioxide (190 mg)

NMR (CDCl₃, δ): 1.34 (1H, t, J=7.0Hz), 1.46 (2H, br),
1.64-1.69 (4H, m), 1.94 (2H, br), 2.07-2.20 (2H,
m), 2.67-2.88 (2H, m), 3.06 (2H, s), 3.11-3.16 (2H,
m), 3.30-3.48 (1H, m), 3.60-3.70 (1H, m), 4.23 (2H,
15 q, J=7.0Hz), 4.53 (1/2H, br), 4.81 (1/2H, br),
6.69 (1H, s), 7.27-7.32 (5H, m), 7.64 (1H, s),
8.05 (1/2H, s), 8.20 (1/2H, s)

MS (ESI-): 535.2 (M-H)

20 Example 331

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(n-
propoxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-
2H-thiopyran-2-acetamide 1,1-dioxide (170 mg)

NMR (CDCl₃, δ): 0.99 (3H, t, J=6.0Hz), 1.45 (2H, br),
25 1.63-1.75 (6H, m), 1.95 (2H, br), 2.06-2.21 (2H,
m), 2.63-2.91 (2H, m), 3.05 (2H, s), 3.12 (2H, br),
3.28-3.50 (1H, m), 3.58-3.69 (1H, m), 4.07-4.15
(2H, m), 4.52 (1/2H, br), 4.80 (1/2H, br), 6.65
(1H, s), 7.20-7.30 (5H, m), 7.66 (1H, s), 7.96
30 (1/2H, s), 8.12 (1/2H, s)

MS (ESI-): 549.4 (M-H)

Example 332

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
35 (isopropoxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-

tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

NMR (CDCl₃, δ): 1.31 (6H, d, J=7.5Hz), 1.45 (2H, br),
1.64-1.68 (4H, m), 1.94 (2H, br), 2.05-2.21 (4H,
m), 2.64-2.86 (2H, m), 3.05 (2H, s), 3.10-3.15 (2H,
m), 3.30-3.38 (1H, m), 3.60-3.70 (1H, m), 4.52
(1/2H, br), 4.80 (1/2H, br), 5.02 (1H, qq, J=7.5,
7.5Hz), 6.59 (1H, s), 7.24-7.28 (5H, m), 7.67 (1H,
s), 7.94 (1/2H, s), 8.10 (1/2H, s)

MS (ESI-): 549.4 (M-H)

Example 333

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-chloroethoxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (155 mg)

NMR (CDCl₃, δ): 1.45 (2H, br), 1.62-1.68 (4H, m), 1.95
(2H, br), 2.07-2.22 (2H, m), 2.63-2.89 (2H, m),
3.05 (2H, s), 3.10-3.16 (2H, m), 3.28-3.48 (1H, m),
3.61-3.66 (1H, m), 3.75 (2H, t, J=5.0Hz), 4.43 (2H,
t, J=5.0Hz), 4.52 (1/2H, br), 4.80 (1/2H, br),
6.80 (1H, s), 7.23-7.31 (5H, m), 7.65 (1H, s),
8.02 (1/2H, s), 8.17 (1/2H, s)

MS (ESI-): 569.3 (M-H)

Example 334

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(valerylaminophenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (148 mg)

NMR (CDCl₃, δ): 0.96 (3H, t, J=7Hz), 1.32-1.78 (12H, m),
1.85-1.99 (2H, m), 2.03-2.25 (2H, m), 2.40 (2H, t,
J=7Hz), 2.69-2.93 (2H, m), 2.98-3.18 (2H, m),
3.28-3.51 (1H, m), 3.62-3.77 (1H, m), 4.55, 4.83
(1H, s), 7.10-7.32 (4H, m), 7.47-7.69 (3H, m),
8.66 (1H, s)

MS (ESI-): 547 (M-H)

Example 335

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(ethylthiocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (130 mg)

5 NMR (CDCl₃, δ): 1.26 (3H, t, J=8Hz), 1.39-1.77 (8H, m),
1.34-2.00 (2H, m), 2.06-2.75 (2H, m), 2.71-2.96
(2H, m), 2.99 (2H, q, J=8Hz), 3.04-3.17 (2H, m),
3.29-3.52 (2H, m), 3.64-3.76 (1H, m), 4.55, 4.84
(1H, s), 7.15-7.32 (4H, m), 7.38-7.54 (3H, m),
10 8.49, 8.58 (1H, s)

MS (ESI-): 551 (M-H)

Example 336

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(methylthiocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (192 mg)

15 NMR (CDCl₃, δ): 1.36-1.78 (8H, m), 1.86-2.00 (2H, m),
2.07-2.75 (2H, m), 2.43, 2.45 (3H, s), 2.72-2.97
(2H, m), 3.03-3.22 (2H, m), 3.30-3.54 (1H, m),
20 3.64-3.76 (1H, m), 4.56, 4.74 (1H, br s), 7.12-
7.32 (4H, m), 7.40-7.53 (2H, m), 7.62-7.71 (1H, m),
8.65, 8.72 (1H, s)

MS (ESI-): 537 (M-H)

Example 337

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(benzyloxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (87 mg)

30 NMR (CDCl₃, δ): 1.35-1.72 (8H, m), 1.86-1.98 (2H, m),
2.02-2.22 (2H, m), 2.65-2.92 (2H, m), 2.98-3.16
(2H, m), 3.28-3.50 (1H, m), 3.62-3.73 (1H, m),
4.52, 4.71 (1H, s), 5.21 (2H, s), 6.88 (1H, br s),
7.19-7.46 (10H, m), 7.62 (1H, br s), 8.26, 8.38
(1H, s)

35 MS (ESI-): 597 (M-H)

Example 338

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(4-chlorophenyl)acetylaminophenyl)-2-thienyl]-3,4,5,6-

5 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (158 mg)

NMR (CDCl₃, δ): 1.35-1.79 (8H, m), 1.87-1.99 (2H, m),
2.04-2.24 (2H, m), 2.17-2.93 (1H, m), 3.02-3.17
(2H, m), 3.27-3.52 (1H, m), 3.63-3.74 (1H, m),
4.53, 4.82 (1H, s), 4.59 (2H, s), 6.83 (1H, d,
10 J=8Hz), 6.96 (2H, d, J=8Hz), 7.22-7.39 (5H, m),
7.56-7.62 (1H, m), 7.22-7.28 (1H, m), 8.30 (1H, s),
8.34, 8.45 (1H, s)

MS (ESI⁺): 633, 634 (M+H)

15 Example 339

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(phenoxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-
2H-thiopyran-2-acetamide 1,1-dioxide (124 mg)

NMR (CDCl₃, δ): 1.34 (8H, m), 1.85-1.99 (2H, m),
20 2.03-2.24 (2H, m), 2.68-2.94 (2H, m), 3.00-3.20
(2H, m), 3.29-3.53 (1H, m), 3.62-3.77 (1H, m),
4.53, 4.82 (1H, s), 7.11-7.47 (11H, m), 7.63, 7.67
(1H, s), 8.49, 8.57 (1H, s)

MS (ESI⁻): 583 (M-H)

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Example 340

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(4-morpholinocarbonylamino)acetylaminophenyl)-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (85
30 mg)

NMR (DMSO-d₆, δ): 1.32-2.09 (10H, m), 2.34-2.51 (1H, m),
2.87-3.62 (14H, m), 3.73-3.92 (1H, m), 3.80 (2H, d,
J=7Hz), 4.43, 4.76 (1H, s), 6.96 (1H, t, J=7Hz),
7.17-7.26 (1H, m), 7.32-7.53 (4H, m), 8.02 (1H, s)

35 MS (ESI⁻): 633 (M-H)

Example 341

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(N-ethyl-N-methylaminocarbonyloxy)acetyl amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg) was obtained in a similar manner to that of Example 211.

NMR (CDCl₃, δ): 1.18, 1.23 (3H, t, J=8Hz), 1.37-1.74 (8H, m), 1.89-2.01 (2H, m), 2.06-2.23 (2H, m), 2.72-2.88 (2H, m), 2.99, 3.03 (3H, s), 3.05-3.18 (2H, m), 3.15-3.28 (1H, m), 4.53, 4.83 (1H, s), 4.72, 4.74 (2H, s), 7.15-7.32 (4H, m), 7.52 (1H, br s), 7.59, 7.64 (1H, br s), 8.23 (1H, s), 8.62-8.75 (1H, m)

MS (ESI-): 606 (M-H)

The following compounds were obtained in a similar manner to that of Example 129.

Example 342

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(benzylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (80 mg)

NMR (CDCl₃, δ): 1.42 (2H, br), 1.60-1.66 (4H, m), 1.83-1.90 (2H, m), 2.00-2.18 (2H, m), 2.74 (2H, br), 2.92-3.00 (2H, m), 3.04-3.10 (2H, m), 3.30-3.50 (1H, m), 3.68-3.78 (1H, m), 4.33-4.42 (2H, m), 4.57 (1/2H, br), 4.72 (1/2H, br), 6.93-7.12 (6H, m), 7.27-7.25 (2H, m), 7.28-7.32 (4H, m)

MS (ESI-): 596.4 (M-H)

Example 343

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(4-methoxyphenylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (224 mg)

NMR (CDCl₃, δ): 1.43 (2H, br), 1.62-1.73 (4H, m), 1.90

(2H, br), 2.03-2.20 (2H, m), 2.77 (2H, br), 2.96-3.03 (2H, m), 3.08-3.14 (2H, m), 3.33-3.54 (1H, m), 3.68-3.75 (1H, m), 3.77 (3H, s), 4.61 (1/2H, br), 4.86 (1/2H, br), 6.80-6.93 (4H, m), 7.10-7.29 (6H, m), 7.38-7.53 (2H, m), 9.04 (1/2H, s), 9.42 (1/2H, s)

MS (ESI-): 611.5 (M-H)

Example 344

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(ethoxycarbonylmethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (490 mg)

NMR (CDCl₃, δ): 1.22-1.33 (5H, m), 1.42-1.47 (2H, m), 1.62-1.70 (2H, m), 1.94 (2H, br), 2.07-2.20 (2H, m), 2.74-2.86 (2H, m), 3.08-3.20 (2H, m), 3.49-3.52 (2H, m), 3.68-3.78 (2H, m), 3.97-4.27 (4H, m), 4.58 (1/2H, br), 4.85 (1/2H, br), 5.68-5.80 (1H, m), 6.96-7.24 (5H, m), 7.28-7.34 (1H, m), 7.40-7.46 (1H, m), 9.12 (1/2H, s), 9.31 (1/2H, s)

MS (ESI-): 592.3 (M-H)

Example 345

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(butylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (330 mg)

NMR (CDCl₃, δ): 0.90 (3H, dd, J=7.2, 7.2Hz), 1.26-1.74 (10H, m), 1.85-1.99 (2H, m), 2.02-2.21 (2H, m), 2.74-2.89 (2H, m), 2.97-3.26 (6H, m), 3.31-3.54 (1H, m), 3.71-3.80 (1H, m), 4.60, 4.83 (1H, s), 5.42-5.53 (1H, m), 6.95 (1H, d, J=4Hz), 7.01-7.30 (5H, m), 7.38-7.43 (1H, m), 9.3, 9.51 (1H, s)

Example 346

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(1-naphtylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-

tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (350 mg)

NMR (CDCl₃, δ): 1.30-1.65 (6H, m), 1.75-1.92 (2H, m),
1.93-2.19 (2H, m), 2.70-2.88 (2H, m), 2.92-3.20
(4H, m), 3.30-3.46 (1H, m), 3.70 (1H, br), 4.56,
4.83 (1H, s), 6.93-7.80 (12H, m), 7.95 (1H, dd,
J=8.0, 8.0Hz)

Example 347

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
(allylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (300 mg)

NMR (CDCl₃, δ): 1.35-1.70 (6H, m), 1.85-2.25 (4H, m),
2.75-2.88 (2H, m), 2.95-3.17 (4H, m), 3.30-3.52
(1H, m), 3.70-3.90 (3H, m), 4.59, 4.83 (1H, s),
5.10-5.23 (2H, m), 5.40-5.49 (1H, m), 5.80-5.94
(1H, m), 6.95-7.28 (6H, m)

MS (ESI-): 546 (M-H)

Example 348

To a solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-
(3-aminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-
2-acetamide 1,1-dioxide (150 mg) and thienylamine (163 mg)
in N,N-dimethylformamide (3 ml) was added 3-
(phenoxycarbonylamino)pyridine (83 mg) and the reaction
mixture was stirred at ambient temperature for 14 hours.
The mixture was poured into water and extracted with ethyl
acetate. The organic layer was washed with water, saturated
aqueous sodium hydrogen carbonate and brine, dried over
anhydrous magnesium sulfate and concentrated in vacuo. The
residue was purified by flash column chromatography on
silica gel 60 (eluent: 3% methanol-chloroform) to give (2S)-
N-(2-tetrahydropyranyloxy)-2-[5-(3-(3-
pyridylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg) as
a white amorphous.

NMR (CDCl₃, δ): 1.38 (2H, br), 1.45-1.62 (4H, m), 1.94 (4H, br), 2.05-2.25 (2H, m), 2.92 (2H, br), 3.02-3.11 (4H, m), 3.32-3.50 (1H, m), 3.78 (1H, br), 4.20-4.23 (1H, m), 4.62 (1/2H, br), 4.94 (1/2H, br), 6.89-7.27 (4H, m), 7.30-7.46 (1H, m), 7.51-7.72 (2H, m), 8.03-8.21 (1H, m), 8.40 (1/2H, s), 8.45 (1/2H, s)

MS (ESI+): 585.4 (M+H)

The following compounds were obtained in a similar manner to that of Example 130.

Example 349

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(allyloxycarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

NMR (CDCl₃, δ): 1.45 (2H, br), 1.58-1.68 (4H, m), 1.94 (2H, br), 2.07-2.22 (2H, m), 2.66-2.90 (2H, m), 3.04-3.52 (2H, m), 3.09-3.15 (2H, m), 3.30-3.49 (1H, m), 3.63-3.72 (1H, m), 4.52 (1/2H, br), 4.67 (2H, d, J=7.0Hz), 4.80 (1/2H, br), 5.27 (1H, d, J=8.0Hz), 5.38 (1H, d, J=8.0Hz), 5.89-6.04 (1H, m), 6.83 (1H, s), 7.24-7.34 (5H, m), 7.63 (1H, s), 8.20 (1/2H, s), 8.35 (1/2H, s)

MS (ESI-): 547.3 (M-H)

Example 350

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-benzyloxyacetyl amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (410 mg)

NMR (CDCl₃, δ): 1.45 (2H, br), 1.61-1.68 (4H, m), 1.95 (2H, br), 2.06-2.22 (2H, m), 2.64-2.87 (2H, m), 3.03 (2H, br s), 3.08-3.13 (2H, m), 3.28-3.47 (1H, m), 3.61-3.67 (1H, m), 4.08 (2H, d, J=7.5Hz), 4.52 (1/2H, br), 4.63 (1H, s), 4.68 (1H, s), 4.67 (2H,

d, J=15Hz), 4.82 (1/2H, br), 7.30-7.40 (9H, m),
7.53 (1H, d, J=5.0Hz), 7.77 (1H, s), 8.01 (1H, s),
8.16 (1H, s), 8.34 (1H, s)

MS (ESI-): 611.5 (M-H)

5

The following compounds were obtained in a similar manner to that of Example 211.

Example 351

10 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(((2S)-2-(tert-butoxycarbonylamino)propionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (310 mg)

15 NMR (CDCl₃, δ): 1.43-1.48 (14H, m), 1.65-1.68 (4H, m), 1.94 (42H, br), 2.04-2.20 (2H, m), 2.67-2.87 (2H, m), 3.04-3.07 (2H, m), 3.10-3.15 (2H, m), 3.28-3.62 (1H, m), 3.63-3.75 (1H, m), 4.32 (1H, br), 4.52 (1/2H, br), 4.82 (1/2H, br), 7.20-7.30 (4H, m), 7.40-7.50 (1H, m), 7.67 (1/2H, s), 7.77 (1/2H, s), 8.36 (1/2H, s), 8.54 (1/2H, s)

20

MS (ESI-): 634.3 (M-H)

Example 352

25 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(((2R)-2-(tert-butoxycarbonylamino)propionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (475 mg)

30 NMR (CDCl₃, δ): 1.43-1.48 (14H, m), 1.65-1.68 (4H, m), 1.94 (42H, br), 2.04-2.20 (2H, m), 2.67-2.87 (2H, m), 3.04-3.07 (2H, m), 3.10-3.15 (2H, m), 3.28-3.62 (1H, m), 3.63-3.75 (1H, m), 4.32 (1H, br), 4.52 (1/2H, br), 4.82 (1/2H, br), 7.20-7.30 (4H, m), 7.40-7.50 (1H, m), 7.67 (1/2H, s), 7.77 (1/2H, s), 8.36 (1/2H, s), 8.54 (1/2H, s)

35

MS (ESI-): 634.3 (M-H)

Example 353

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(4-methylphenoxy)acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

NMR (CDCl₃, δ): 1.44 (2H, br), 1.56-1.68 (4H, m), 1.95 (2H, br), 2.07-2.21 (2H, m), 2.33 (3H, s), 2.63-2.90 (2H, m), 3.05 (2H, s), 3.11-3.13 (2H, br), 3.30-3.48 (1H, m), 3.60-3.70 (1H, m), 4.52 (1/2H, br), 4.60 (2H, s), 4.80 (1/2H, br), 6.90 (2H, d, J=8.0Hz), 7.15 (2H, d, J=8.0Hz), 7.22-7.29 (2H, m), 7.33-7.36 (2H, m), 7.55-7.59 (1H, m), 7.80 (1H, s), 8.00 (1/2H, s), 8.14 (1/2H, s), 8.32 (1H, s)

MS (ESI-): 611.3 (M-H)

Example 354

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(N,N-dimethylamino)acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (90 mg)

NMR (CDCl₃, δ): 1.46 (2H, br), 1.62-1.68 (4H, m), 1.95 (4H, br), 2.04-2.23 (2H, m), 2.41 (6H, s), 2.65-2.88 (1H, m), 3.05 (2H, s), 3.10 (2H, m), 3.12-3.15 (2H, m), 3.26-3.49 (1H, m), 3.62-3.72 (1H, m), 4.52 (1/2H, br), 4.80 (1/2H, br), 7.23-7.29 (2H, m), 7.34 (2H, d, J=5.0Hz), 7.60-7.66 (1H, m), 7.76 (1H, br), 8.00 (1/2H, br), 8.18 (1/2H, br), 9.19 (1H, s)

MS (ESI+): 550.3 (M+H)

Example 355

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(4-chlorophenyl)acetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (158 mg)

NMR (CDCl₃, δ): 1.34-1.98 (10H, m), 2.03-2.25 (2H, m), 2.69-2.88 (2H, m), 3.02-3.18 (2H, m), 3.27-3.51

(1H, m), 3.62-3.26 (1H, m), 3.68 (2H, s), 4.53, 4.83 (1H, br s), 7.00-7.66 (10H, m), 7.73, 7.76 (1H, s), 8.65-8.75 (1H, m)

MS (ESI-): 616 (M-H)

5

Example 356

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-((R)-2-tert-butoxycarbonylamino-2-phenylacetyl)amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (117 mg)

10

NMR (DMSO-d₆, δ): 1.20-1.62 (6H, m), 1.40 (9H, s), 1.68-2.06 (4H, m), 2.34-2.48 (1H, m), 2.86-3.32 (5H, m), 3.73-3.86 (1H, m), 4.40, 4.75 (1H, br s), 5.86 (1H, d, J=8Hz), 7.16-7.23 (1H, m), 7.28-7.61 (10H, m), 7.96 (1H, s), 10.37 (1H, s), 11.23 (1H, s)

15

MS (ESI-): 696 (M-H)

Example 357

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-isopropoxyacetyl)amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (276 mg)

20

NMR (CDCl₃, δ): 1.29 (6H, d, J=7Hz), 1.36-1.77 (8H, m), 1.88-2.00 (2H, m), 2.65-2.92 (2H, m), 3.02-3.18 (2H, m), 3.28-3.51 (1H, m), 3.62-3.73 (1H, m), 3.77 (1H, q, J=7Hz), 4.07 (1H, s), 4.52, 4.82 (1H, br s), 7.23-7.48 (4H, m), 7.52-7.60 (1H, m), 7.78 (1H, s), 8.18, 8.32 (1H, br s), 8.40 (1H, s)

25

MS (ESI+): 565 (M+H)

Example 358

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-((1-tert-butoxycarbonyl-4-piperidinyloxy)acetyl)amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (360 mg)

30

NMR (CDCl₃, δ): 1.40-1.77 (10H, m), 1.47 (9H, s), 1.89-

2.01 (4H, m), 2.06-2.24 (2H, m), 2.68-2.92 (2H, m),
3.02-3.18 (4H, m), 3.28-3.52 (1H, m), 3.58-3.74
(2H, m), 3.79-3.92 (2H, m), 4.12 (2H, m), 4.53,
4.82 (1H, s), 7.22-7.38 (4H, m), 7.52-7.58 (1H, m),
5 7.76 (1H, s), 8.27, 8.84 (1H, s), 8.34, 8.38 (1H,
s)

MS (ESI+): 706 (M+H)

Example 359

10 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(2-oxo-1,3-
oxazolidin-3-yl)acetyl amino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (600 mg)

NMR (DMSO-d₆, δ): 1.36-1.64 (6H, m), 1.69-2.06 (4H, m),
2.34-2.48 (1H, m), 2.88-3.32 (5H, m), 3.42-3.53
15 (1H, m), 3.66 (2H, t, J=8Hz), 3.73-3.90 (1H, m),
4.34 (2H, t, J=8Hz), 4.44, 4.75 (1H, s), 7.17-7.25
(1H, m), 7.33-7.48 (4H, m), 8.03 (1H, s)

MS (ESI-): 590 (M-H)

20 Example 360

To a suspension of (2S)-N-(2-tetrahydropyranyloxy)-2-
[5-(3-aminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (300 mg) and triethylamine
(392 mg) in chloroform (4 ml) was added triphosgene (192 mg)
25 at 0°C and the reaction mixture was stirred at ambient
temperature for 30 minutes. To the mixture was added (2-
((tert-butyl)(diphenyl)silyloxy)ethyl)amine (232 mg) at 0°C
and the reaction mixture was stirred at ambient temperature
for 2 hours. The mixture was poured into water and was
30 extracted with chloroform. The organic layer was washed
with water, 10% aqueous citric acid solution, saturated
aqueous sodium hydrogen carbonate and brine, dried over
anhydrous magnesium sulfate and concentrated in vacuo. The
residue was purified by flash column chromatography on
35 silica gel 60 (eluent: 2% methanol-chloroform) to give (2S)-

N-(2-tetrahydropyranyloxy)-2-[5-(3-(2-((tert-butyl)(diphenyl)silyloxy)ethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (350 mg) as a white amorphous.

5 NMR (CDCl₃, δ): 1.04 (9H, s), 1.44 (2H, br), 1.62-1.68 (4H, m), 1.85-1.94 (2H, br), 2.05-2.19 (2H, m), 2.69-2.90 (2H, m), 2.98-3.10 (4H, m), 3.31-3.44 (3H, m), 3.62-3.80 (3H, m), 4.56 (1/2H, br), 4.80 (1/2H, br), 6.64 (1H, s), 7.09-7.30 (5H, m), 7.32-7.42 (7H, m), 7.56-7.64 (4H, m), 8.62 (1H, s)
10 MS (ESI-): 788.5 (M-H)

The following compounds were obtained in a similar manner to that of Example 130.

15 Example 361

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(cyclopentylcarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (205 mg)

20 NMR (CDCl₃, δ): 1.46 (2H, br), 1.60-1.70 (6H, m), 1.77-1.84 (2H, m), 1.91-1.97 (6H, m), 2.07-2.21 (2H, m), 2.66-2.89 (2H, m), 2.71 (1H, tt, J=7.5, 7.5Hz), 3.05 (1H, s), 3.10-3.15 (2H, m), 3.30-3.49 (1H, m), 3.63-3.70 (1H, m), 4.54 (1/2H, br), 4.82 (1/2H, br), 7.20-7.30 (4H, m), 7.41 (2H, br), 7.52 (1H, br), 7.71 (1H, br), 8.25 (1/2H, s), 8.37 (1/2H, s)
25 MS (ESI-): 559.4 (M-H)

Example 362

30 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(3-chloropropionylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (145 mg)

NMR (CDCl₃, δ): 1.45 (2H, br), 1.54-1.72 (4H, m), 1.95 (4H, br), 2.09-2.24 (2H, m), 2.72-2.82 (2H, m), 2.85 (2H, t, J=6.4Hz), 3.00-3.08 (2H, m), 3.11-
35

3.16 (2H, m), 3.29-3.52 (1H, m), 3.63-3.73 (1H, m),
3.91 (2H, t, J=6.5Hz), 4.54 (1/2H, br), 4.83 (1/2H,
br), 7.15-7.30 (4H, m), 7.54-7.72 (3H, m), 8.50
(1H, s)

5 MS (ESI-): 553.3 (M-H)

The following compounds were obtained in a similar
manner to that of Example 360.

10 Example 363

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
(isobutylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

15 NMR (CDCl₃, δ): 0.90 (6H, d, J=6.6Hz), 1.40-1.70 (7H,
m), 1.88-1.97 (2H, m), 2.05-2.22 (2H, m), 2.99-
3.18 (6H, m), 3.31-3.51 (1H, m), 6.96-7.29 (6H, m),
7.47-7.53 (1H, m), 9.25, 9.47 (1H, s)

MS (ESI-): 562 (M-H)

20 Example 364

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(cyclohexyl-
methylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)

25 NMR (CDCl₃, δ): 0.83-1.00 (2H, m), 1.10-1.25 (4H, m),
1.35-1.54 (5H, m), 1.55-1.79 (6H, m), 1.85-1.98
(2H, m), 2.01-2.22 (2H, m), 2.75-2.89 (2H, m),
3.00-3.22 (6H, m), 3.30-3.52 (1H, m), 3.66-3.82
(1H, m), 1.59, 4.84 (1H, s), 5.45-5.55 (1H, m),
6.95-7.30 (6H, m), 7.40 (1H, br)

30

Example 365

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-
methoxyethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg)

35 NMR (CDCl₃, δ): 1.38-1.68 (6H, m), 1.85-1.98 (2H, m),

2.03-2.18 (2H, m), 2.75-2.90 (2H, m), 3.01-3.17
(4H, m), 3.30-3.35 (1H, m), 3.38 (3H, s), 3.42-
3.55 (4H, m), 3.66-3.77 (1H, m), 4.55, 4.84 (1H,
s), 5.51-5.60 (1H, m), 7.05-7.40 (6H, m), 9.10,
9.20 (1H, s)

MS (ESI-): 564 (M-H)

Example 366

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-((N-methyl-N-
ethylaminocarbonyl)amino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)

NMR (CDCl₃, δ): 1.33 (3H, t, J=7.0Hz), 1.40-1.75 (6H,
m), 1.85-1.98 (2H, m), 2.05-2.20 (2H, m), 2.60-
2.90 (4H, m), 3.00-3.20 (5H, m), 3.29-3.50 (1H, m),
3.62-3.73 (1H, m), 4.23 (2H, q, J=7.0Hz), 4.53,
4.80 (1H, s), 7.15-7.35 (6H, m)

MS (ESI-): 548 (M-H)

Example 367

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-((2-
phthalimidoethoxy)carbonylamino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (155 mg)
from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-aminophenyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (300 mg) and 2-phthaloyl ethanol

NMR (CDCl₃, δ): 1.42-1.70 (6H, m), 1.81-1.96 (2H, m),
2.02-2.23 (2H, m), 2.87-3.27 (4H, m), 3.49 (2H,
br), 3.52-3.75 (2H, m), 4.04 (2H, br), 4.16-4.48
(1H, m), 5.05-5.23 (1H, m), 6.76-7.36 (8H, m),
7.66-7.74 (2H, m), 7.79-7.87 (2H, m)

MS (ESI-): 680.5 (M-H)

The following compounds were obtained in a similar
manner to that of Example 32.

Example 368

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-phenylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

5 NMR (DMSO-d₆, δ): 1.38-1.62 (6H, m), 1.72-2.06 (4H, m),
2.38-2.47 (1H, m), 2.90-3.52 (6H, m), 3.75-3.90
(1H, m), 4.45, 4.75 (1H, s), 6.86 (1H, d, J=16Hz),
7.06 (1H, dd, J=8.0, 8.0Hz), 7.24-7.27 (1H, m),
7.34 (2H, d, J=8.0, 8.0Hz), 7.55-7.58 (2H, m),
10 7.65-7.76 (6H, m)

Example 369

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-(4-methoxy-phenylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

15 NMR (DMSO-d₆, δ): 1.37-1.64 (6H, m), 1.71-2.08 (4H, m),
2.36-2.47 (1H, m), 2.90-3.51 (6H, m), 3.74 (3H, s),
3.75-3.90 (1H, m), 4.45, 4.75 (1H, s), 6.82 (1H, d,
J=16Hz), 6.92 (2H, d, J=8.5Hz), 7.24-7.27 (1H, m),
20 7.54-7.75 (8H, m)

Example 370

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-(4-fluoro-phenylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

25 NMR (DMSO-d₆, δ): 1.37-1.62 (6H, m), 1.70-2.08 (4H, m),
2.36-2.46 (1H, m), 2.91-3.54 (6H, m), 3.75-3.90
(1H, m), 4.45, 4.75 (1H, s), 6.83 (1H, d, J=16Hz),
7.18 (2H, dd, J=8.5, 8.5Hz), 7.24-7.27 (1H, m),
30 7.55-7.75 (8H, m), 10.3 (1H, s)

Example 371

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-(N,N-dimethylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (250 mg)

35

NMR (CDCl₃, δ): 1.35-1.75 (6H, m), 1.88-2.01 (2H, m),
2.05-2.25 (2H, m), 2.65-3.18 (9H, m), 3.20 (3H, s),
3.26-3.49 (1H, m), 3.64-3.70 (1H, m), 4.54, 4.83
(1H, s), 6.91 (1H, d, J=16Hz), 7.29 (1H, d,
J=4.0Hz), 7.47-7.69 (6H, m)

Example 372

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-(
(isopropylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg)

NMR (DMSO-d₆, δ): 1.11 (6H, d, J=5Hz), 1.37-1.64 (6H,
m), 1.70-2.07 (4H, m), 2.35-2.46 (1H, m), 2.90-
3.37 (5H, m), 3.40-3.54 (1H, m), 3.74-3.90 (1H, m),
3.90-4.01 (1H, m), 4.45, 4.75 (1H, s), 6.62 (1H, d,
J=16Hz), 7.21-7.25 (1H, m), 7.40 (1H, d, J=16Hz),
7.51-7.55 (1H, m), 7.57 (2H, d, J=8.5Hz), 7.69 (2H,
d, J=8.5Hz), 7.99 (1H, d, J=7.5Hz)

Example 373

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(2-(
(propylaminocarbonyl)ethenyl)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (210 mg)

NMR (DMSO-d₆, δ): 0.88 (3H, t, J=7.5Hz), 1.36-1.62 (8H,
m), 1.70-2.06 (4H, m), 2.35-2.45 (1H, m), 2.40-
3.30 (7H, m), 3.41-3.52 (1H, m), 3.74-3.90 (1H, m),
4.45, 4.75 (1H, s), 6.65 (1H, d, J=16Hz), 7.22-
7.25 (1H, m), 7.40 (1H, d, J=16Hz), 7.51-7.55 (1H,
m), 7.60 (2H, d, J=8.5Hz), 7.70 (2H, d, J=8.5Hz),
8.10 (1H, t, J=7.0Hz), 11.2 (1H, s)

Example 374

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(n-
propylaminocarbonylmethoxy)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (140 mg)

NMR (DMSO-d₃, δ): 0.82 (3H, t, J=7.5Hz), 1.36-1.63 (8H,

5 m), 1.70-2.05 (4H, m), 2.33-2.44 (1H, m), 2.93-3.50 (8H, m), 3.74-3.91 (1H, m), 4.45, 4.75 (1H, s), 4.50 (2H, s), 7.01 (2H, d, J=8.5Hz), 7.16-7.20 (1H, m), 7.33-7.37 (1H, m), 7.58 (2H, d, J=8.5Hz), 8.10 (1H, br)

Example 375

To a suspension of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-((2-phthalimidoethoxy)carbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (155 mg) in methanol (4 ml) was added hydrazine monohydrate (13.7 mg) and the reaction mixture was stirred at ambient temperature for 3 hours, the resulting mixture was filtrated and washed with methanol. The filtrate was concentrated in vacuo to give (2S)-N-(2-tetrahydro-pyranyloxy)-2-[5-(3-(2-aminoethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (125 mg) as a white amorphous.

20 NMR (CDCl₃, δ): 1.24-1.35 (2H, m), 1.42-1.52 (2H, m), 1.62-1.73 (2H, m), 1.96 (2H, br), 2.08-2.25 (2H, m), 2.86 (2H, br), 3.01-3.05 (2H, m), 3.15 (2H, br), 3.44-3.50 (4H, m), 3.74-3.84 (1H, m), 4.22-4.25 (1H, m), 4.45 (1/2H, br), 4.83 (1/2H, br), 7.22-7.30 (4H, m), 7.37-7.44 (1H, m), 7.68 (1H, br s), 7.83-7.86 (1H, m), 8.20-8.24 (1H, m)

25 MS (ESI+): 552.3 (M+H)

The following compounds were obtained in a similar manner to that of Example 130.

Example 376

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(ethylcarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

35 NMR (DMSO-d₆, δ): 1.15 (3H, dd, J=7.5, 7.5Hz), 1.38-1.61

(6H, m), 1.70-2.07 (4H, m), 2.37-2.46 (1H, m),
2.58-2.66 (2H, m), 2.90-3.51 (6H, m), 3.75-3.88
(1H, m), 4.43, 4.75 (1H, s), 7.18-7.25 (3H, m),
7.43-7.48 (1H, m), 7.68 (2H, d, J=8.5Hz)

5 MS (ESI-): 520 (M-H)

Example 377

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
(methoxyacetoxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
10 thiopyran-2-acetamide 1,1-dioxide (150 mg)

NMR (DMSO-d₆, δ): 1.36-1.62 (6H, m), 1.69-2.05 (4H, m),
2.34-2.43 (1H, m), 2.87-3.29 (5H, m), 3.38 (3H, s),
3.40-3.51 (1H, m), 3.75-3.90 (1H, m), 4.37 (2H, s),
4.44, 4.75 (1H, s), 7.20-7.26 (3H, m), 7.42-7.48
15 (1H, m), 7.70 (2H, d, J=8.5Hz)

MS (ESI-): 536 (M-H)

Example 378

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
20 (ethoxycarbonyloxyphenyl)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg)

NMR (DMSO-d₆, δ): 1.30 (3H, dd, J=7.5, 7.5Hz), 1.38-1.65
(6H, m), 1.70-1.95 (4H, m), 2.36-2.45 (1H, m),
2.90-3.51 (6H, m), 3.72-3.90 (1H, m), 4.27 (2H,
25 ddd, J=7.5, 7.5, 7.5Hz), 7.43, 4.75 (1H, s), 7.20-
7.26 (1H, m), 7.29 (2H, d, J=8.5Hz), 7.45-7.49 (1H,
m), 7.69 (2H, d, J=8.5Hz)

MS (ESI-): 536 (M-H)

30 The following compounds were obtained in a similar
manner to that of Example 129.

Example 379

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-
35 (methylaminocarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-

tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (250 mg)

NMR (DMSO-d₆, δ): 1.37-1.62 (4H, m), 1.70-2.05 (4H, m),
2.35-2.46 (1H, m), 2.67 (3H, d, J=4.5Hz), 2.90-
3.30 (5H, m), 3.40-3.55 (1H, m), 3.75-3.88 (1H, m),
4.44, 4.75 (1H, s), 7.15 (2H, d, J=8.7Hz), 7.18-
7.24 (1H, m), 7.40-7.45 (1H, m), 7.63 (2H, d,
J=8.7Hz)

MS (ESI-): 521 (M-H)

10 Example 380

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(ethylaminocarbonyloxy)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

NMR (CDCl₃, δ): 1.23 (3H, dd, J=7.2, 7.2Hz), 1.36-1.75
(6H, m), 1.86-2.00 (2H, m), 2.03-2.25 (2H, m),
2.65-2.87 (2H, m), 3.01-3.18 (4H, m), 3.26-3.37
(2H, m), 3.60-3.69 (1H, m), 4.51, 4.80 (1H, s),
5.01-5.09 (1H, m), 7.14 (2H, d, J=8.7Hz), 7.16-
7.25 (2H, m), 7.54 (2H, d, J=8.7Hz), 8.09, 8.24
(1H, s)

MS (ESI-): 535 (M-H)

Example 381

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-hydroxyphenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (1 g) was obtained in a similar manner to that of Example 201.

NMR (CDCl₃, δ): 1.38-1.66 (6H, m), 1.70-2.04 (4H, m),
1.84-1.94 (1H, m), 2.89-3.48 (6H, m), 3.75-3.90
(1H, m), 4.45, 4.75 (1H, s), 8.80 (2H, d, J=8.7Hz),
7.13-7.17 (1H, m), 7.21-7.25 (1H, m), 7.45 (2H, d,
J=8.7Hz), 9.68 (1H, s)

The following compounds were obtained in a similar
manner to that of Example 201.

Example 382

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(6-methyl-3-pyridyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (99 mg)

NMR (CDCl₃, δ): 1.40-1.75 (6H, m), 1.90-2.00 (2H, m), 2.07-2.25 (2H, m), 2.59 (3H, s), 2.70-2.94 (2H, m), 3.05-3.17 (4H, m), 3.30-3.52 (1H, m), 3.63-3.74 (1H, m), 4.52 (0.5H, s), 4.81 (0.5H, s), 7.17 (2H, d, J=8Hz), 7.26-7.33 (2H, m), 7.75 (1H, dd, J=1.5, 8Hz), 8.12 (0.5H, s), 8.24 (0.5, s), 8.74 (1H, d, J=1.5Hz)

MS (ESI-): 463 (M-H)

Example 383

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(6-methyl-3-pyridyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg)

NMR (CDCl₃, δ): 1.40-1.74 (6H, m), 1.88-2.00 (2H, m), 2.07-2.20 (2H, m), 2.67-2.87 (2H, m), 3.04-3.08 (2H, m), 3.09-3.18 (2H, m), 3.30-3.52 (1H, m), 3.60-3.73 (1H, m), 3.96 (3H, s), 4.53 (0.5H, s), 4.81 (0.5H, s), 6.77 (1H, d, J=8Hz), 6.83 (1H, d, J=8Hz), 7.16-7.20 (1H, m), 7.64-7.79 (1H, m), 7.99 (0.5H, s), 8.13 (0.5H, s), 8.39-8.42 (1H, m)

MS (ESI-): 479 (M-H)

The following compounds were obtained in a similar manner to that of Example 130.

Example 384

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (105 mg)

NMR (CDCl₃, δ): 1.33-1.77 (8H, m), 1.87-2.00 (2H, m),

2.11 (3H, m), 2.06-2.77 (2H, m), 2.85-3.36 (5H, m),
3.66-3.83 (2H, m), 4.36-4.48 (1H, m), 4.53 (1/2H,
br), 4.88 (1/2H, br), 7.12-7.37 (5H, m), 7.59-7.67
(1H, m), 8.82 (1/2H, br s), 8.84 (1/2H, br s),
9.83 (1H, s), 10.04 (1H, s)

5

MS (ESI-): 563.0 (M-H)

Example 385

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(3-
(methoxycarbonyl)propionylamino)phenyl}-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (130 mg)

10

NMR (CDCl₃, δ): 1.44 (4H, br), 1.65-1.67 (2H, m), 1.95
(2H, br), 2.08-2.21 (2H, m), 2.67-2.77 (6H, m),
3.06-3.14 (4H, m), 3.29-3.48 (1H, m), 3.62-3.70
(1H, m), 3.72 (3H, s), 4.53 (1/2H, br), 4.81 (1/2H,
br), 7.20-7.27 (3H, m), 7.51 (1H, br), 7.60 (1/2H,
s), 7.66 (1/2H, s), 7.80 (1/2H, br), 7.84 (1/2H,
br), 8.40 (1/2H, s), 8.44 (1/2H, s)

15

MS (ESI-): 577.2 (M-H)

20

Example 386

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(N-
methoxycarbonyl-N-methylamino)acetylaminophenyl)-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (160 mg)

25

NMR (CDCl₃, δ): 1.46 (2H, br), 1.68 (4H, br), 1.96 (2H,
br), 2.07-2.24 (2H, m), 2.70-2.94 (2H, m), 3.02-
3.09 (2H, m), 3.10 (3H, s), 3.16 (2H, br), 3.31-
3.53 (1H, m), 3.65-3.75 (1H, m), 3.80 (3H, s),
4.02-4.09 (2H, m), 4.54 (1/2H, br), 4.83 (1/2H,
br), 7.24-7.31 (5H, m), 7.53 (1H, br), 7.63 (1/2H,
s), 7.67 (1/2H, s), 8.44 (1/2H, s), 8.50 (1/2H, s)

30

MS (ESI-): 592.1 (M-H)

Example 387

35

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[4-(3-pyridyl-2-propenyloxy)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (270 mg)

5 NMR (DMSO-d₆, δ): 1.36-1.65 (6H, m), 1.70-2.06 (4H, m),
2.36-2.47 (1H, m), 2.91-3.28 (5H, m), 3.41-3.52
(1H, m), 3.75-3.91 (1H, m), 4.45, 4.75 (1H, s),
7.07 (1H, d, J=16Hz), 7.21-7.26 (1H, m), 7.30 (2H,
10 d, J=8.0Hz), 7.45-7.51 (2H, m), 7.72 (2H, d,
J=8.0Hz), 7.94 (1H, d, J=16Hz), 8.28-8.32 (1H, m),
8.60-8.62 (1H, m), 8.99 (1H, s)

MS (ESI-): 595 (M-H)⁺

The following compounds were obtained in a similar manner to that of Example 211.

15 Example 388

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(2-methoxyethoxy)acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (175 mg)

20 NMR (CDCl₃, δ): 1.35-1.74 (8H, m), 1.89-1.99 (2H, m),
2.06-2.25 (2H, m), 2.68-2.89 (2H, m), 3.02-3.17
(2H, m), 3.25-3.46 (1H, m), 3.52 (3H, s), 3.58-
3.67 (2H, m), 3.74-3.81 (2H, m), 4.13 (2H, s),
4.52 (1/2H, br), 4.79 (1/2H, br), 7.22-7.38 (4H,
25 m), 7.55-7.62 (1H, m), 7.83 (1H, br s), 8.04 (1/2H,
s), 8.19 (1/2H, s), 8.97 (1H, s)

MS (ESI-): 579.9 (M-H)

30 Example 389

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(N-9-fluorenylmethoxycarbonyl-N-methylamino)acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (1.77 g)

35 NMR (CDCl₃, δ): 1.42 (2H, br), 1.64 (4H, br), 1.95 (2H,
br), 2.08-2.23 (2H, m), 2.70-2.90 (2H, m), 3.00-

3.07 (5H, m), 3.10-3.16 (2H, m), 3.27-3.48 (1H, m),
3.60-3.70 (1H, m), 4.00-4.09 (1H, m), 4.28 (1H,
br), 4.52 (2H, s), 4.56 (1/2H, br), 4.80 (1/2H,
br), 7.21-7.48 (9H, m), 7.58-7.65 (3H, m), 7.75
(2H, br), 8.20 (1/2H, s), 8.32 (1/2H, s)

MS (ESI-): 791.9 (M-H+Cl)

Example 390

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(((2S)-2,6-
bis(tert-butoxycarbonylamino)hexanoyl)amino)phenyl}-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (290 mg)

NMR (CDCl₃, δ): 1.45 (18H, s), 1.48-1.70 (14H, m), 1.95
(2H, br), 2.09-2.20 (2H, m), 2.68-2.92 (2H, m),
3.00-3.15 (4H, m), 3.25-3.49 (1H, m), 3.63-3.74
(1H, m), 4.16-4.28 (1H, m), 4.52 (1/2H, br), 4.65
(1/2H, br), 7.22-7.24 (2H, m), 7.27-7.30 (2H, m),
7.51 (1H, br), 7.62-7.82 (1H, m)

MS (ESI-): 791.3 (M-H)

Example 391

(2S)-N-(2-Tetrahydropyranyloxy)-2-5-{3-(2-tert-
butoxycarbonylamino-3-(3-pyridyl)propionylamino)phenyl}-2-
thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-
dioxide (1.54 g)

NMR (DMSO-d₆, δ): 1.22-1.27 (2H, m), 1.43 (9H, s), 1.63-
1.68 (4H, m), 1.98 (2H, br), 2.07-2.25 (2H, m),
2.74-2.98 (2H, m), 3.04-3.20 (6H, m), 3.41-3.48
(1H, m), 3.66-3.76 (1H, m), 4.45 (1/2H, br), 4.54-
4.63 (1H, br), 4.86 (1/2H, br), 5.31-5.45 (1H, m),
6.82-7.00 (2H, m), 7.04-7.20 (3H, m), 7.22-7.27
(2H, m), 7.52-7.65 (2H, m), 8.43-8.59 (3H, m)

MS (ESI+): 713.1 (M+H)

Example 392

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(3-carboxypropionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (50 mg) was obtained in a similar manner to that of Example 3.

5 NMR (DMSO-d₆, δ): 1.36-2.06 (10H, m), 2.34-2.63 (5H, m), 2.88-3.52 (6H, m), 3.65-3.90 (1H, m), 4.43 (1/2H, br), 4.75 (1/2H, br), 7.17-7.32 (1H, m), 7.28-7.48 (4H, m), 8.00 (1H, s), 10.08 (1H, s), 10.59 (1H, s), 11.22 (1H, s), 12.13 (1H, br s)

10 MS (ESI-): 563.4 (M-H)

Example 393

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(3-(methylaminocarbonyl)propionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (50 mg) was obtained in a similar manner to that of Example 32.

15 NMR (CDCl₃, δ): 1.48 (2H, br), 1.62 (4H, br), 1.96 (2H, br), 2.06-2.26 (2H, m), 2.62-2.66 (2H, m), 2.75 (3H, br s), 2.88 (2H, br), 3.05-3.22 (5H, m), 3.36-3.49 (1H, m), 3.73-3.99 (1H, m), 4.15-4.25 (1H, m), 4.70 (1/2H, s), 4.95 (1/2H, s), 6.97-7.12 (4H, m), 7.32-7.43 (2H, m), 9.12 (1/2H, br), 9.24 (1/2H, br)

20 MS (ESI-): 576.3 (M-H)

25

Example 394

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(tert-butoxycarbonylaminomethyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg) was obtained in a similar manner to that of Example 89.

30 NMR (CDCl₃, δ): 1.47 (9H, s), 1.52-1.68 (6H, m), 1.81-1.95 (2H, m), 2.06-2.23 (2H, m), 2.63-2.89 (2H, m), 3.05 (2H, br s), 3.08-3.13 (2H, m), 3.27-3.50 (1H, m), 3.61-3.70 (1H, m), 4.24-4.39 (2H, m), 4.52 (1/2H, br), 4.80 (1/2H, br), 6.71-6.82 (1H,

35

m), 7.14-7.70 (5H, m), 8.07 (1/2H, s), 8.24 (1/2H, s)

MS (ESI-): 577.3 (M-H)

5 Example 395

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(methylamino)acetylaminophenyl)-2-thienyl}-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (915 mg) was obtained in a similar manner to that of Example 239.

10 NMR (DMSO-d₆, δ): 1.42-1.59 (6H, m), 1.73-2.05 (4H, m),
2.32 (3H, s), 2.37-2.46 (1H, m), 2.89-3.20 (4H, m),
3.25 (2H, s), 3.42-3.48 (2H, m), 3.75-3.78 (1H, m),
4.44 (1/2H, br), 4.75 (1/2H, br), 7.20-7.24 (1H,
m), 7.34-7.36 (2H, m), 7.38-7.42 (1H, m), 7.55-
15 7.57 (1H, m), 8.02 (1H, s)

MS (ESI+): 536.3 (M+H)

The following compounds were obtained in a similar manner to that of Example 54.

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Example 396

(2S)-N-Hydroxy-2-[5-(6-methyl-3-pyridyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (89 mg)

25 NMR (DMSO-d₆, δ): 1.71-2.10 (4H, m), 2.35-2.54 (1H, m),
2.68 (3H, s), 2.96-3.08 (2H, m), 3.14-3.60 (3H, m),
7.32 (1H, d, J=3.5Hz), 7.74-7.81 (2H, m), 8.49 (1H,
dd, J=1.5, 8Hz), 9.01 (1H, d, J=1.5Hz), 10.66 (1H,
s)

30 MS (ESI-): 379 (M-H)

Example 397

(2S)-N-Hydroxy-2-[5-(6-methoxy-3-pyridyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide, 1,1-dioxide (50
35 mg)

NMR (DMSO-d₆, δ): 1.71-2.09 (4H, m), 2.33-2.52 (1H, m),
2.95-3.08 (2H, m), 3.10-3.29 (2H, m), 3.42-3.58
(1H, m), 3.89 (3H, s), 6.89 (1H, d, J=8Hz), 7.21
(1H, d, J=3.5Hz), 7.43 (1H, d, J=3.5Hz), 7.97 (1H,
5 dd, J=1.5, 8Hz), 8.47 (1H, d, J=1.5Hz)

MS (ESI-): 395 (M-H)

Example 398

(2S)-N-Hydroxy-2-[5-[4-(5-methyl-1,2,4-oxadiazol-3-
10 yl)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (67 mg)

NMR (DMSO-d₆, δ): 1.71-2.09 (4H, m), 2.20-2.52 (1H, m),
2.68 (3H, s), 2.94-3.08 (2H, m), 3.11-3.33 (2H, m),
3.36-3.56 (1H, m), 7.26 (1H, d, J=3.5), 7.63 (1H,
15 d, J=3.5Hz), 7.84 (2H, d, J=8Hz), 8.03 (2H, d,
J=8Hz), 8.84 (1H, s)

MS (ESI-): 446 (M-H)

Example 399

(2S)-N-Hydroxy-2-[5-{3-(2-(acetylamino)acetylamino)-
20 phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (75 mg)

NMR (DMSO-d₆, δ): 1.69-2.08 (4H, m), 1.89 (3H, s),
2.34-2.48 (1H, m), 2.94-3.30 (4H, m), 3.38-3.55
25 (1H, m), 3.88 (2H, d, J=8.0Hz), 7.21 (1H, d,
J=4.0Hz), 7.32-7.40 (2H, m), 7.42 (1H, d, J=4.0Hz),
7.44-7.51 (1H, m), 7.98 (1H, s), 8.22 (1H, t,
J=8.0Hz), 8.83 (1H, s), 10.08 (1H, s), 10.60 (1H,
s)

30 MS (ESI-): 478.3 (M-H)

Example 400

(2S)-N-Hydroxy-2-[5-{3-(3-methoxycarbonylpropionyl-
amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
35 acetamide 1,1-dioxide (60 mg)

NMR (DMSO-d₆, δ): 1.72-2.09 (4H, m), 2.33-2.48 (1H, m),
2.63 (3H, s), 2.77-3.40 (6H, m), 3.42-3.55 (1H, m),
7.21 (1H, d, J=4.0Hz), 7.28-7.48 (4H, m), 7.98 (1H,
s), 8.84 (1H, s), 10.12 (1H, s), 10.60 (1H, s)

MS (ESI-): 493.4 (M-H)

Example 401

(2S)-N-Hydroxy-2-[5-{3-(3-(methylaminocarbonyl)-
propionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (30 mg)

NMR (DMSO-d₆, δ): 1.73-2.05 (4H, m), 2.40 (2H, t,
J=6.0Hz), 2.45-2.49 (1H, m), 2.53-2.58 (3H, m),
2.95-3.26 (4H, m), 3.40-3.54 (3H, m), 7.20 (1H, d,
J=4.0Hz), 7.32 (2H, d, J=4.5Hz), 7.39 (1H, d,
J=4.0Hz), 7.43-7.47 (2H, m), 7.82 (1H, br), 8.00
(1H, s), 10.08 (1H, s), 10.60 (1H, s)

MS (ESI-): 492.1 (M-H)

Example 402

(2S)-N-Hydroxy-2-[5-{3-(2-(2-methoxyethoxy)-
acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (120 mg)

NMR (DMSO-d₆, δ): 1.70-2.07 (4H, m), 2.36-2.46 (1H, m),
2.94-3.28 (4H, m), 3.31 (3H, s), 3.48-3.51 (1H, m),
3.52-3.58 (2H, m), 3.66-3.72 (2H, m), 4.10 (2H, s),
7.22 (1H, d, J=4.0Hz), 7.33-7.40 (1H, m), 7.40 (1H,
d, J=4.0Hz), 7.52-7.62 (1H, m), 8.00 (1H, s), 8.84
(1H, s), 9.76 (1H, s), 10.60 (1H, s)

MS (ESI-): 495.3 (M-H)

Example 403

(2S)-N-Hydroxy-2-[5-(3-aminomethylphenyl)-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (132
mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(tert-
butoxycarbonylamino methyl)phenyl)-2-thienyl]-3,4,5,6-

tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO₆, δ): 1.73-2.08 (4H, m), 2.35-2.45 (1H, m).

2.95-3.26 (4H, m), 3.43-3.55 (1H, m), 4.08 (2H,

br), 7.24 (1H, d, J=4.0Hz), 7.37-7.39 (1H, m),

7.45-7.50 (2H, m), 7.68 (1H, d, J=7.5Hz), 7.75 (1H,

s), 8.15 (2H, br), 8.83 (1H, s), 10.60 (1H, s)

MS (ESI-): 435.2 (M-H+CH₃CN)

Example 404

(2S)-N-Hydroxy-2-[5-{3-(2-(N-methoxycarbonyl-N-methylamino)acetylaminophenyl)-2-thienyl}-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (110 mg)

NMR (DMSO-d₆, δ): 1.75-2.06 (4H, m), 2.37-2.46 (1H, m),

2.90 (3/2H, s), 2.94 (3/2H, s), 2.95-3.26 (4H, m),

3.40-3.50 (1H, m), 3.56 (3/2H, s), 3.63 (3/2H, s),

4.05 (2H, s), 7.20 (1H, d, J=4.0Hz), 7.32-7.39 (3H,

m), 7.42 (1H, d, J=4.0Hz), 8.02 (1H, s), 8.84 (1H,

s)

MS (ESI-): 508.4 (M-H)

Example 405

(2S)-N-Hydroxy-2-[5-{3-(((2S)-2,6-diaminohexanoyl)-amino)phenyl)-2-thienyl}-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-{3-(((2S)-2,6-bis(tert-butoxycarbonylamino)hexanoyl)amino)phenyl)-2-thienyl}-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.33-1.44 (2H, m), 1.50-1.60 (2H, m),

1.73-1.93 (4H, m), 1.95-2.07 (1H, m), 2.35-2.45

(1H, m), 2.73-2.80 (2H, m), 2.95-3.28 (4H, m),

3.50-3.55 (1H, m), 3.94 (1H, br), 7.22 (1H, d,

J=4.0Hz), 7.42-7.45 (3H, m), 7.53 (1H, d, J=7.0Hz),

7.94 (1H, s), 8.38 (1H, s)

MS (ESI+): 509.3 (M+H)

Example 406

(2S)-N-Hydroxy-2-[5-{3-(2-amino-3-(3-pyridyl)-propionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (460 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-{3-(2-tert-butoxycarbonylamino-3-(3-pyridyl)propionylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.74-2.07 (4H, m), 2.36-2.46 (1H, m), 2.96-3.32 (6H, m), 3.45-3.55 (1H, m), 4.24 (1H, br), 7.22 (1H, d, J=4.0Hz), 7.39-7.48 (4H, m), 7.52-7.57 (1H, m), 7.83-7.88 (2H, m), 8.39 (2H, br), 8.56-8.60 (2H, m), 10.57 (1H, s), 10.60 (1H, s)

MS (ESI+): 529.1 (M+H)

Example 407

(2S)-N-Hydroxy-2-[5-(4-(3-pyridyl-2-propenyloxy)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (180 mg)

NMR (DMSO-d₆, δ): 1.70-2.06 (4H, m), 2.36-2.47 (1H, m), 2.96-3.56 (5H, m), 7.16 (1H, d, J=16Hz), 7.23 (1H, d, J=4.0Hz), 7.30 (2H, d, J=8.5Hz), 7.49 (1H, d, J=16Hz), 7.70-7.76 (3H, m), 7.97 (1H, d, J=8.5Hz), 8.53-8.57 (1H, m), 8.75 (1H, d, J=5Hz), 9.12 (1H, s), 10.6 (1H, s)

MS (ESI-): 511 (M-H)

Example 408

To a solution of (2S)-2-tert-butoxycarbonylamino-3-hydroxypropionic acid (66 mg), 1-hydroxybenzotriazole (44 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (62 mg) in N,N-dimethylformamide (1.3 ml) was added a solution of (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-aminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-

acetamide 1,1-dioxide (100 mg) in N,N-dimethylformamide (0.5 ml) at ambient temperature. After being stirred at the same temperature overnight, the reaction mixture was added ethyl acetate and the solution was washed successively with water, a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and evaporated under a stream of nitrogen. After the residue was dissolved in methanol (1 ml), the solution was added 4N hydrogen chloride in ethyl acetate. The mixture was stirred at ambient temperature for 1 hour. After the solution was evaporated under a stream of nitrogen, the residue was purified by reverse phase HPLC (0.1% trifluoroacetic acid in acetonitrile, 1-60% gradient) to give (2S)-N-hydroxy-2-[5-{3-((2S)-2-amino-3-hydroxypropionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (30 mg) as a white powder.

NMR (DMSO-d₆, δ): 1.76-2.10 (4H, m), 2.38-2.46 (1H, m), 3.00 (2H, d, J=10Hz), 3.13-3.52 (4H, m), 3.82-3.93 (1H, m), 3.98-4.06 (1H, m), 7.23 (1H, d, J=4.0Hz), 7.40-7.45 (3H, m), 7.50-7.54 (1H, m), 7.98 (1H, s), 8.32 (2H, br), 10.73 (1H, s)

MS (ESI+): 468.3 (M+H)

The following compound was obtained in a similar manner to that of Example 408.

Example 409

(2S)-N-Hydroxy-2-[5-{3-(2-dimethylaminocarbonyl)amino)-acetylaminophenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (30 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-{3-((2-aminoacetyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (150 mg) and dimethylaminocarbonyl chloride.

NMR (DMSO-d₆, δ): 1.74-2.04 (4H, m), 2.35-2.44 (1H, m),

2.85 (6H, s), 2.95-3.25 (4H, m), 3.46-3.53 (1H, m),
3.78 (2H, d, J=4.0Hz), 6.65 (1H, t, J=4.0Hz), 7.20
(1H, d, J=4.0Hz), 7.34-7.40 (2H, m), 7.40-7.48 (2H,
m), 8.01 (1H, s), 8.08 (1H, br), 9.98 (1H, s),
10.60 (1H, s)

MS (ESI+): 509.2 (M+H)

Example 410

(2S)-N-Hydroxy-2-[5-{3-(2-(N-(dimethylaminocarbonyl)-N-methylamino)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (30 mg) was obtained in a similar manner to that of Example 409.

NMR (DMSO-d₆, δ): 1.73-2.05 (4H, m), 2.37-2.48 (1H, m),
2.74 (6H, s), 2.87 (3H, s), 2.95-3.25 (4H, m),
3.44-3.52 (1H, m), 3.91 (2H, s), 7.20 (1H, d,
J=4.0Hz), 7.34-7.45 (3H, m), 7.42 (1H, d, J=4.0Hz),
8.02 (1H, s), 10.06 (1H, s), 10.60 (1H, s)

MS (ESI-): 521.2 (M-H)

Example 411

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (113 mg) was obtained in a similar manner to that of Example 201.

NMR (CDCl₃, δ): 1.38-1.74 (6H, m), 1.90-2.01 (2H, m),
2.06-2.25 (2H, m), 2.67 (3H, s), 2.70-2.89 (2H, m),
3.03-3.08 (2H, m), 3.10-3.18 (2H, m), 3.28-3.50
(1H, m), 3.59-3.72 (1H, m), 4.53 (0.5H, s), 4.81
(0.5H, s), 7.28-7.32 (1H, m), 7.35-7.39 (1H, m),
7.71 (2H, d, J=8Hz), 7.99 (0.5H, s), 8.08 (2H, d,
J=8Hz), 8.13 (0.5H, s)

MS (ESI-): 530 (M-H)

Example 412

tert-Butyl 2-(5-bromo-2-thienyl)-2,3,4,5-tetrahydrothiophene-2-acetate (2.77 g) was obtained in substantially the same manner as that of Example 93.

5 NMR (CDCl₃, δ): 1.34 (9H, s), 1.90-2.05 (1H, m),
2.07-2.20 (2H, m), 2.26-2.36 (1H, m), 2.83 (1H, d,
J=15Hz), 2.98-3.09 (2H, m), 3.12 (1H, d, J=15Hz),
6.70 (1H, d, J=4Hz), 6.87 (2H, d, J=4Hz)

Example 413

10 tert-Butyl 2-[5-(4-fluorophenyl)-2-thienyl]-2,3,4,5-tetrahydrothiophene-2-acetate (479 mg) was obtained in substantially the same manner as that of Example 100.

15 NMR (CDCl₃, δ): 1.34 (9H, s), 2.02-2.29 (3H, m), 2.36-2.46 (1H, m), 3.00 (1H, d, J=16Hz), 3.01-3.14 (2H, m), 3.17 (1H, d, J=16Hz), 6.92 (1H, d, J=4Hz),
7.00-7.08 (3H, m), 7.52 (2H, dd, J=4, 9Hz)

Example 414

20 2-[5-(4-Fluorophenyl)-2-thienyl]-2,3,4,5-tetrahydrothiophene-2-acetic acid (298 mg) was obtained in a similar manner to that of Example 95.

25 NMR (CDCl₃, δ): 2.02-2.31 (3H, m), 2.39-2.50 (1H, m),
2.98-3.17 (3H, m), 3.30 (1H, d, J=16Hz), 6.93 (1H, d, J=4Hz), 6.99-7.08 (3H, m), 7.50 (2H, dd, J=5, 9Hz)

MS (ESI-): 321 (M-H)

Example 415

30 2-[5-(4-Fluorophenyl)-2-thienyl]-2,3,4,5-tetrahydrothiophene-2-acetic acid 1,1-dioxide (272 mg) was obtained in a similar manner to that of Preparation 1-4).

35 NMR (CDCl₃, δ): 2.18-2.43 (2H, m), 2.70-2.82 (1H, m),
2.89-3.01 (1H, m), 3.09 (1H, d, J=16Hz), 3.14-3.25 (2H, m), 3.36 (1H, d, J=16Hz), 7.07 (2H, t, J=9Hz),
7.13-7.18 (2H, m), 7.54 (2H, dd, J=5, 9Hz)

The following compounds were obtained in a similar manner to that of Example 130.

5 Example 416

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(benzyloxycarbonylamino)acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (230 mg)

10 NMR (CDCl₃, δ): 1.43 (4H, br), 1.63-1.65 (2H, m), 1.94 (2H, br), 2.09-2.23 (2H, m), 2.82 (2H, br), 3.06-3.17 (4H, m), 3.27-3.50 (1H, m), 3.64-3.76 (1H, m), 4.03-4.05 (2H, m), 4.52 (1/2H, br), 4.83 (1/2H, br), 5.18 (2H, s), 7.10-7.22 (4H, m), 7.30-7.38
15 (6H, m), 7.45-7.55 (2H, m), 8.23 (1H, br), 8.77 (1/2H, br), 8.85 (1/2H, br)

MS (ESI-): 654.2 (M-H)

Example 417

20 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(4-methoxybenzenesulfonylamino)acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (220 mg)

NMR (CDCl₃, δ): 1.43 (4H, br), 1.62-1.72 (2H, m), 1.95 (2H, br), 2.06-2.25 (2H, m), 2.75-2.90 (2H, m),
25 3.00-3.18 (4H, m), 3.28-3.50 (1H, m), 3.64-3.70 (1H, m), 3.75 (2H, d, J=6.0Hz), 3.82 (3H, s), 4.54 (1/2H, br), 4.85 (1/2H, br), 5.72-5.86 (1H, m), 6.98 (2H, d, J=8.0Hz), 7.14-7.23 (4H, m), 7.85 (2H,
30 d, J=8.0Hz), 8.40 (1H, br), 8.78 (1/2H, s), 8.94 (1/2H, s)

MS (ESI-): 690.1 (M-H)

Example 418

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[3-[2-(1,5,5-

trimethylhydantoin-3-yl)acetylamino]phenyl]-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (212
mg) was obtained in a similar manner to that of Example 211.

NMR (CDCl₃, δ): 1.38-1.75 (12H, m), 1.87-2.05 (2H, m),
2.07-2.28 (2H, m), 2.77-2.96 (5H, m), 3.00-3.25
(4H, m), 3.27-3.54 (1H, m), 3.68-3.81 (1H, m),
4.40 (2H, s), 4.53 (0.5H, s), 4.85 (0.5H, s),
6.93-7.06 (1H, m), 7.09-7.34 (4H, m), 7.54-7.66
(1H, m), 8.25-8.35 (1H, m), 9.05 (0.5H, s), 9.20
(0.5H, s)

MS (ESI-): 645 (M-H)

Example 419

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[4-
(phenoxy carbonyloxymethyl)phenyl]-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg) was
obtained in a similar manner to that of Example 244.

NMR (CDCl₃, δ): 1.35-1.76 (6H, m), 1.87-2.00 (2H, m),
2.04-2.25 (2H, m), 2.65-2.91 (2H, m), 3.00-3.18
(4H, m), 3.25-3.51 (1H, m), 3.59-3.72 (1H, m),
4.53 (0.5H, s), 4.81 (0.5H, s), 5.27 (2H, s), 7.17
(2H, d, J=8Hz), 7.23-7.32 (1H, m), 7.35-7.49 (6H,
m), 7.62 (2H, d, J=8Hz), 8.01 (0.5H, s), 8.15
(0.5H, s)

MS (ESI-): 598 (M-H)

Example 420

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[4-
(methylaminocarbonyloxymethyl)phenyl]-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg) was
obtained in a similar manner to that of Example 245.

NMR (CDCl₃, δ): 1.36-1.75 (6H, m), 1.86-2.01 (2H, m),
2.05-2.24 (2H, m), 2.64-2.85 (5H, m), 3.01-3.18
(4H, m), 3.27-3.50 (1H, m), 3.56-3.70 (1H, m),
4.53 (0.5H, s), 4.61-4.74 (1H, m), 4.80 (0.5H, s),

5.11 (2H, s), 7.21-7.29 (2H, m), 7.36 (2H, d, J=8Hz), 7.56 (2H, d, J=8Hz), 7.96 (0.5H, s), 8.11 (0.5H, s)

MS (ESI-): 535 (M-H)

5

Example 421

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[5-(methoxycarbonylamino)-3-pyridyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (170 mg) was obtained in a similar manner to that of Example 201.

10

NMR (CDCl₃, δ): 1.40-1.74 (6H, m), 1.89-2.01 (2H, m), 2.05-2.25 (2H, m), 2.70-2.95 (2H, m), 3.01-3.17 (4H, m), 3.30-3.56 (1H, m), 3.62-3.76 (1H, m), 3.83 (3H, s), 4.53 (0.5H, s), 4.84 (0.5H, s), 6.97-7.06 (1H, m), 7.25-7.33 (1H, m), 7.36-7.65 (1H, m), 8.10-8.19 (1H, m), 8.40-8.56 (3H, m)

15

MS (ESI-): 522 (M-H)

Example 422

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(methylaminocarbonylmethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (45 mg) was obtained in a similar manner to that of Example 32.

20

NMR (CDCl₃, δ): 1.40-1.47 (4H, m), 1.64-1.69 (2H, m), 2.15 (2H, br), 2.28 (2H, br), 2.80 (3H, br s), 2.81-2.88 (2H, m), 2.98-3.15 (4H, m), 3.25-3.52 (1H, m), 3.72-3.81 (1H, m), 3.85-3.94 (2H, m), 4.50 (1/2H, br), 4.85 (1/2H, br), 5.27-5.43 (1H, m), 7.12-7.19 (6H, m), 7.48-7.55 (2H, m), 7.67-7.72 (1H, m)

25

30

MS (ESI-): 577.2 (M-H)

Example 423

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-

35

(carboxymethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (130 mg) was obtained in a similar manner to that of Example 3.

5 NMR (CDCl₃, δ): 1.43-1.50 (2H, m), 1.64-1.68 (4H, m),
1.92 (2H, br), 2.08-2.21 (2H, m), 2.40-2.48 (2H,
m), 2.95-3.14 (4H, m), 3.30-3.53 (1H, m), 3.75-
3.81 (1H, m), 4.00 (2H, br s), 4.45 (1/2H, br),
4.82 (1/2H, br), 7.15-7.22 (5H, m), 7.53 (1/2H, s),
7.57 (1/2H, s)
10 MS (ESI-): 565.0 (M-H)

The following compounds were obtained in a similar manner to that of Example 249.

15 Example 424

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(allylamino)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (106 mg)

20 NMR (CDCl₃, δ): 1.45 (2H, br), 1.64-1.68 (4H, m), 1.95
(2H, br), 2.06-2.24 (2H, m), 2.64-2.86 (2H, m),
3.07 (2H, br s), 3.13-3.16 (2H, m), 3.30-3.49 (1H,
m), 3.46 (3H, d, J=7.0Hz), 3.45 (2H, s), 3.62-3.71
(1H, m), 4.52 (1/2H, s), 4.80 (1/2H, s), 5.20-5.30
(2H, m), 5.85-5.98 (1H, m), 7.23-7.32 (4H, m),
25 7.56 (1H, br), 7.80 (1H, s), 9.40 (1H, s)
MS (ESI+): 562.2 (M+H)

Example 425

30 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(2-ethoxyethylamino)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (65 mg)

NMR (CDCl₃, δ): 1.23 (3H, t, J=7.5Hz), 1.46 (2H, br),
1.65-1.80 (4H, m), 1.95 (2H, br), 2.05-2.25 (2H,
m), 2.65-2.85 (1H, m), 2.88 (2H, t, J=6.0Hz),
35 3.30-3.49 (1H, m), 3.44 (2H, s), 3.51-3.58 (4H, m),

3.62-3.70 (1H, m), 4.52 (1/2H, br), 4.80 (1/2H, br), 7.27-7.35 (5H, m), 7.57-7.61 (1H, m), 7.83 (1H, s), 8.03 (1/2H, br), 8.20 (1/2H, br s), 9.52 (1H, s)

5 MS (ESI+): 594.2 (M+H)

Example 426

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(benzylamino)acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (95 mg)

10 NMR (CDCl₃, δ): 1.43 (2H, br), 1.52-1.68 (4H, m), 1.96 (2H, br), 2.10-2.22 (2H, m), 2.66-2.89 (2H, m), 3.06 (2H, br s), 3.10-3.16 (2H, m), 3.29-3.50 (1H, m), 3.45 (2H, br s), 3.60-3.70 (1H, m), 3.88 (2H, s), 4.52 (1/2H, br), 4.80 (1/2H, br), 7.27-7.38 (10H, m), 7.52 (1H, br), 7.79 (1H, br), 8.05 (1/2H, br), 8.20 (1/2H, br), 9.33 (1H, s)

15

MS (ESI+): 612.2 (M+H)

20 Example 427

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(pentylamino)acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (83 mg)

25 NMR (CDCl₃, δ): 0.87-0.94 (5H, m), 1.29-1.64 (6H, m), 1.42-1.64 (4H, m), 1.95 (2H, br), 2.08-2.22 (2H, m), 2.62-2.88 (2H, m), 2.69 (2H, t, J=7.0Hz), 3.06 (2H, s), 3.10-3.14 (2H, m), 3.24-3.50 (1H, m), 3.39 (2H, s), 3.61-3.69 (1H, m), 4.54 (1/2H, br), 4.80 (1/2H, br), 7.25-7.33 (5H, m), 7.56 (1H, br), 7.80 (1H, s), 8.00 (1/2H, br), 8.16 (1/2H, s), 9.44 (1H, s)

30

MS (ESI+): 592.3 (M+H)

Example 428

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-((2R)-2-tert-

butoxycarbonylamino-3-benzyloxypropionyl)aminophenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (400 mg)

5 NMR (CDCl₃, δ): 1.40-1.48 (2H, br), 1.49 (9H, s),
1.60-1.68 (4H, m), 1.94 (2H, br), 2.06-2.24 (2H, m), 2.65-2.90 (2H, m), 3.06 (1H, br s), 3.11-3.16 (2H, br), 3.27-3.47 (1H, m), 3.63-3.70 (2H, m), 3.97-4.04 (1H, m), 4.44 (1H, br), 4.52 (1/2H, br), 4.55 (1H, d, J=11.0Hz), 4.65 (1H, d, J=11.0Hz),
10 4.80 (1/2H, br), 5.50 (1H, br), 7.22-7.41 (11H, m), 7.72 (1H, br), 8.07 (1/2H, s), 8.20 (1/2H, s), 8.47 (1H, br)

MS (ESI-): 776.2 (M-H+Cl)

15 The following compounds were obtained in a similar manner to that of Example 54.

Example 429

20 (2S)-N-Hydroxy-2-[5-(3-cyclobutanecarbonylamino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (250 mg)

NMR (DMSO-d₆, δ): 1.75-2.30 (10H, m), 2.37-2.46 (1H, m), 2.95-3.52 (5H, m), 7.20 (1H, d, J=4.0Hz), 7.33-7.35 (2H, m), 7.40 (1H, d, J=4.0Hz), 7.46-
25 7.50 (1H, m), 8.02 (1H, s), 9.84 (1H, s), 10.60 (1H, s)

MS (ESI-): 461 (M-H)

Example 430

30 (2S)-Hydroxy-2-[5-[3-[2-(1,5,5-trimethylhydantoin-3-yl)acetyl]amino]phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (117 mg)

NMR (DMSO-d₆, δ): 1.36 (6H, s), 1.70-2.09 (4H, m), 2.35-2.54 (1H, m), 2.84 (3H, s), 2.94-3.08 (2H, m),
35 3.10-3.29 (2H, m), 3.36-3.55 (1H, m), 4.23 (2H, s),

7.21 (1H, d, J=3.5Hz), 7.35-7.43 (4H, m), 7.95 (1H, s), 8.83 (1H, s), 10.41 (1H, s), 10.60 (1H, s)

MS (ESI-): 561 (M-H)

5 Example 431

(2S)-N-Hydroxy-2-[5-[4-(methylaminocarbonyloxymethyl)-phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (46 mg)

10 NMR (DMSO-d₆, δ): 1.67-2.09 (4H, m), 2.34-2.53 (1H, m),
2.59 (3H, d, J=4.8Hz), 2.94-3.08 (2H, m), 3.10-
3.30 (2H, m), 3.38-3.55 (1H, m), 5.02 (2H, s),
7.21 (1H, d, J=3.5Hz), 7.38 (2H, d, J=8Hz), 7.48
(1H, d, J=3.5Hz), 7.64 (2H, d, J=8Hz), 8.85 (1H,
br s)

15 MS (ESI-): 451 (M-H)

Example 432

(2S)-N-Hydroxy-2-[5-[5-(methoxycarbonylamino)-3-pyridyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (94 mg)

20 NMR (DMSO-d₆, δ): 1.71-2.09 (4H, m), 2.35-2.56 (1H, m),
2.95-3.08 (2H, m), 3.11-3.32 (2H, m), 3.41-3.57
(1H, m), 3.74 (3H, s), 7.29 (1H, d, J=3.5Hz), 7.65
(1H, d, J=3.5Hz), 8.32 (1H, s), 8.63 (1H, d,
25 J=1.5Hz), 8.71 (1H, d, J=1.5Hz)

MS (ESI+): 440 (M+H)

Example 433

30 (2S)-N-Hydroxy-2-[5-[3-(2,2-dimethylpropionylamino)-phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg)

35 NMR (DMSO-d₆, δ): 1.24 (9H, s), 1.71-2.08 (4H, m),
2.35-2.53 (1H, m), 2.94-3.07 (2H, m), 3.10-3.28
(2H, m), 3.39-3.55 (1H, m), 7.20 (1H, d, J=3.5Hz),
7.30-7.39 (2H, m), 7.41 (1H, d, J=3.5Hz), 7.59-

7.65 (1H, m), 8.01 (1H, s), 8.84 (1H, br s), 9.30
(1H, s)

MS (ESI-): 463 (M-H)

5 Example 434

(2S)-N-Hydroxy-2-[5-[3-((E)-2-butenoylamino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (104 mg)

10 NMR (DMSO-d₆, δ): 1.71-2.08 (7H, m), 2.36-2.55 (1H, m),
2.94-3.08 (2H, m), 3.10-3.29 (2H, m), 3.39-3.85
(1H, m), 6.14 (1H, dd, J=1.5, 14Hz), 6.75-6.88 (1H,
m), 7.21 (1H, d, J=3.5Hz), 7.32-7.39 (2H, m), 7.41
(1H, d, J=3.5Hz), 7.50-7.56 (1H, m), 8.05 (1H, s),
10.08 (1H, s), 10.60 (1H, s)

15 MS (ESI-): 447 (M-H)

Example 435

20 (2S)-N-Hydroxy-2-[5-{3-(2-(benzyloxycarbonylamino)-
acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (150 mg)

NMR (DMSO-d₆, δ): 1.75-2.06 (4H, m), 2.38-2.47 (1H, m),
2.96-3.27 (4H, m), 3.40-3.55 (1H, m), 3.83 (2H, d,
J=6.5Hz), 5.06 (2H, s), 7.22 (1H, d, J=4.0Hz),
7.29-7.40 (8H, m), 7.45-7.50 (1H, m), 7.58 (1H, t,
25 J=6.5Hz), 8.00 (1H, s), 8.84 (1H, br), 10.10 (1H,
s), 10.60 (1H, br)

MS (ESI-): 570.1 (M-H)

Example 436

30 (2S)-N-Hydroxy-2-[5-{3-(2-(4-methoxybenzenesulfonyl-
amino)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (170 mg)

NMR (DMSO-d₆, δ): 1.73-2.05 (4H, m), 2.35-2.46 (1H, m),
2.95-3.26 (4H, m), 3.49-3.53 (1H, m), 3.62 (2H, s),
35 3.77 (3H, s), 7.08 (2H, d, J=8.0Hz), 7.20 (1H, d,

J=4.0Hz), 7.30-7.38 (4H, m), 7.75 (12H, d, J=8.0Hz), 7.84 (1H, s), 8.84 (1H, br), 10.02 (1H, s)

MS (ESI-): 606.2 (M-H)

5

Example 437

(2S)-N-Hydroxy-2-[5-(3-(methylaminocarbonylmethyl-aminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (25 mg)

10 NMR (DMSO-d₆, δ): 1.72-2.08 (4H, m), 2.36-2.45 (1H, m), 2.61 (3H, d, J=4.5Hz), 2.95-3.25 (4H, m), 3.42-3.50 (1H, m), 3.70 (2H, d, J=6.5Hz), 6.45 (1H, t, J=6.5Hz), 7.17-7.27 (4H, m), 7.37 (1H, d, J=4.0Hz), 7.84 (4H, s), 7.88 (1H, br), 8.84 (1H, br), 9.01
15 (1H, s), 10.63 (1H, s)

MS (ESI-): 493.3 (M-H)

Example 438

(2S)-N-Hydroxy-2-[5-{3-(((2R)-2-amino-3-benzyloxypropionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (125 mg) from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(3-(((2R)-2-tert-butoxycarbonylamino-3-benzyloxypropionyl)amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

25 NMR (DMSO-d₆, δ): 1.73-2.06 (4H, m), 2.36-2.46 (1H, m), 2.95-3.26 (4H, m), 3.40-3.55 (1H, m), 3.48 (2H, d, J=4.5Hz), 4.26 (1H, br t, J=4.5Hz), 4.58 (2H, d, J=5.0Hz), 7.23 (1H, d, J=4.0Hz), 7.27-7.35 (6H, m),
30 7.40-7.44 (2H, m), 7.53 (1H, d, J=6.0Hz), 7.94 (1H, s), 8.41 (2H, br), 8.83 (1H, s), 10.62 (1H, s), 10.82 (1H, s)

MS (ESI-): 558.3 (M-H)

35 Example 439

(2S)-N-Hydroxy-2-[5-{3-(2-(allylamino)acetylamino)-phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

5 NMR (DMSO-d₆, δ): 1.75-2.06 (4H, m), 2.36-2.45 (1H, m),
2.96-3.27 (4H, m), 3.40-3.50 (1H, m), 3.69 (2H, d,
J=6.0Hz), 3.93 (2H, s), 5.42-5.54 (2H, m), 5.84-
5.98 (1H, m), 7.22 (1H, d, J=4.0Hz), 7.38-7.45 (3H,
m), 7.48-7.52 (1H, m), 7.95 (1H, s), 8.85 (1H, br),
10.63 (1H, s), 10.77 (1H, s)

10 MS (ESI-): 476.1 (M-H)

Example 440

(2S)-N-Hydroxy-2-[5-{3-(2-(2-ethoxyethylamino)-acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-
15 thiopyran-2-acetamide 1,1-dioxide (45 mg)

NMR (DMSO-d₆, δ): 1.14 (3H, t, J=7.0Hz), 1.74-2.06 (4H,
m), 2.35-2.45 (1H, m), 2.93-3.26 (4H, m), 3.41-
3.47 (1H, m), 3.57 (2H, td, J=7.0, 7.0Hz), 3.55
(2H, t, J=4.5Hz), 3.65 (2H, s), 7.22 (1H, d,
20 J=4.0Hz), 7.38-7.44 (3H, m), 7.50-7.54 (1H, m),
7.98 (1H, s), 8.84 (1H, s), 10.33 (1H, br), 10.62
(1H, s)

MS (ESI-): 508.2 (M-H)

25 Example 441

(2S)-N-Hydroxy-2-[5-{3-(2-pentylamino)acetylamino)-phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (55 mg)

30 NMR (DMSO-d₆, δ): 0.90 (3H, t, J=4.5Hz), 1.24-1.34 (4H,
m), 1.63 (2H, br), 1.73-2.05 (4H, m), 2.37-2.46
(1H, m), 2.92-3.28 (6H, m), 3.43-3.53 (1H, m),
3.92 (2H, s), 7.22 (1H, d, J=4.0Hz), 7.38-7.44 (3H,
m), 7.50-7.54 (1H, m), 7.96 (1H, s), 8.84 (2H, br
s), 10.64 (1H, s), 10.75 (1H, s)

35 MS (ESI+): 508.1 (M+H)

Example 442

(2S)-N-Hydroxy-2-[5-(3-isobutyrylamino-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (250 mg)

NMR (DMSO-d₃, δ): 1.11 (6H, d, J=7.0Hz), 1.70-2.08 (4H, m), 2.35-2.45 (1H, m), 2.55-2.64 (1H, m), 2.95-3.54 (5H, m), 7.20 (1H, d, J=4.0Hz), 7.34-7.35 (2H, m), 7.40 (1H, d, J=4.0Hz), 7.46-7.51 (1H, m), 8.01 (1H, s), 8.84 (1H, s), 9.94 (1H, s), 10.60 (1H, s)

MS (ESI-): 449 (M-H)

Example 443

(2S)-N-Hydroxy-2-[5-{3-(2-benzylamino)acetyl-amino)-phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (55 mg)

NMR (DMSO-d₆, δ): 1.74-2.06 (4H, m), 2.35-2.45 (1H, m), 2.95-3.28 (4H, m), 3.40-3.50 (3H, m), 3.89 (1H, s), 4.24 (1H, s), 7.22 (1H, d, J=4.0Hz), 7.36-7.55 (9H, m), 7.92 (1H, s), 8.84 (1H, s), 10.62 (1H, s), 10.68 (1H, s)

MS (ESI-): 528.1 (M-H)

The following compounds were obtained in a similar manner to that of Example 408.

Example 444

(2S)-N-Hydroxy-2-[5-{3-((2S)-2-amino-3-benzyloxypropionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (40 mg) from L-Boc-Ser(bzl)-OH

NMR (DMSO-d₆, δ): 1.73-2.06 (4H, m), 2.36-2.46 (1H, m), 2.95-3.26 (4H, m), 3.40-3.55 (1H, m), 3.48 (2H, d, J=4.5Hz), 4.26 (1H, br t, J=4.5Hz), 4.58 (2H, d, J=5.0Hz), 7.23 (1H, d, J=4.0Hz), 7.27-7.35 (6H, m),

7.40-7.44 (2H, m), 7.53 (1H, d, J=6.0Hz), 7.94 (1H, s), 8.41 (2H, br), 8.83 (1H, s), 10.62 (1H, s), 10.82 (1H, s)

MS (ESI+): 558.3 (M+H)

5

Example 445

(2S)-N-Hydroxy-2-[5-{3-((2S)-2-pyrrolidinylcarbonyl-amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (40 mg) from L-Boc-Pro-OH

10 NMR (DMSO-d₆, δ): 1.84-2.05 (7H, m), 2.35-2.45 (2H, m), 2.95-3.30 (4H, m), 3.44-3.53 (3H, m), 4.35 (1H, br), 7.22 (1H, d, J=4.0Hz), 7.39-7.50 (4H, m), 7.96 (1H, s), 8.72 (1H, br), 8.83 (1H, s), 9.27 (1H, br)

15 MS (ESI+): 468.3 (M+H)

Example 446

(2S)-N-Hydroxy-2-[5-{3-((2S)-2-amino-3-cyclohexylpropionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (50 mg) from L-Boc-CHA-OH

20 NMR (DMSO-d₆, δ): 0.87-0.98 (2H, m), 1.10-1.25 (4H, m), 1.40 (1H, br), 1.60-1.77 (6H, m), 1.85-2.06 (4H, m), 2.35-2.47 (1H, m), 2.95-3.27 (4H, m), 3.44-3.53 (1H, m), 3.96 (1H, br), 7.22 (1H, d, J=4.0Hz), 7.40-7.48 (3H, m), 7.60 (1H, d, J=7.0Hz), 7.90 (1H, s), 8.23 (2H, br), 8.84 (1H, s), 10.55 (1H, s), 10.60 (1H, s)

25 MS (ESI+): 534.8 (M+H)

30

Example 447

(2S)-N-Hydroxy-2-[5-{3-((2-amino-2-methylpropionyl)-amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (20 mg) from L-Boc-AiB-OH

35 NMR (DMSO-d₆, δ): 1.62 (6H, s), 1.74-2.06 (4H, m),

2.35-2.44 (1H, m), 2.95-3.27 (4H, m), 3.37-3.53
(1H, m), 7.22 (1H, d, J=4.0Hz), 7.38-7.48 (3H, m),
7.60 (1H, d, J=7.5Hz), 7.92 (1H, s), 8.24 (2H, br),
8.83 (1H, s)

5 MS (ESI+): 466.3 (M+H)

Example 448

(2S)-N-Hydroxy-2-[5-{3-(((2R)-2-methoxypropionyl)-
amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
10 acetamide 1,1-dioxide (30 mg)

NMR (DMSO-d₆, δ): 1.32 (3H, d, J=6.0Hz), 1.73-2.06 (4H,
m), 2.36-2.43 (1H, m), 2.95-3.26 (4H, m), 3.34 (3H,
s), 3.45-3.54 (1H, m), 3.87 (1H, q, J=6.0Hz), 7.20
(1H, d, J=4.0Hz), 7.32-7.35 (2H, m), 7.40 (1H, d,
15 J=4.0Hz), 7.62 (1H, d, J=6.5Hz), 8.60 (1H, s),
9.93 (1H, s), 10.60 (1H, s)

MS (ESI-): 465.2 (M-H)

Example 449

20 (2S)-N-Hydroxy-2-[5-{3-(((2S)-2-amino-4-
carboxybutyryl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-
2H-thiopyran-2-acetamide 1,1-dioxide (33 mg) from
L-Boc-Glu(tBu)-OH

NMR (DMSO-d₆, δ): 1.74-2.25 (6H, m), 2.37-2.46 (1H, m),
25 2.95-3.26 (4H, m), 3.45-3.62 (1H, m), 3.95-4.04
(3H, m), 7.23 (1H, d, J=4.0Hz), 7.40-7.45 (3H, m),
7.52 (1H, d, J=7.0Hz), 7.90 (1H, s), 8.28 (2H, br),
8.84 (1H, br)

MS (ESI+): 510.7 (M+H)

30

Example 450

(2S)-N-Hydroxy-2-[5-{3-(2-(benzoylamino)acetyl)-
amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (42 mg)

35 NMR (DMSO-d₆, δ): 1.72-2.04 (4H, m), 2.36-2.47 (1H, m),

2.95-3.25 (4H, m), 3.43-3.53 (1H, m), 4.09 (2H, d, J=6.0Hz), 7.20 (1H, d, J=4.0Hz), 7.36-7.39 (2H, m), 7.42 (1H, d, J=4.0Hz), 7.47-7.57 (4H, m), 7.92 (2H, d, J=7.5Hz), 8.30 (1H, s), 8.88 (1H, t, J=6.0Hz), 10.20 (1H, s), 10.60 (1H, s)

MS (ESI-): 541.3 (M-H)

Example 451

(2S)-N-Hydroxy-2-[5-{3-(2-(ethylamino)acetyl amino)-phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (60 mg) from 2-(N-ethyl-N-tert-butoxycarbonylamino)acetic acid

NMR (DMSO-d₆, δ): 1.22 (3H, t, J=7.0Hz), 1.74-2.06 (4H, m), 2.35-2.45 (1H, m), 2.95-3.27 (6H, m), 3.51-3.57 (1H, m), 3.96 (2H, t, J=5.0Hz), 7.22 (1H, d, J=4.0Hz), 7.42-7.46 (3H, m), 7.48-7.51 (1H, m), 7.93 (1H, s), 8.87 (2H, br), 10.60 (1H, s), 10.54 (1H, s)

MS (ESI+): 466.2 (M+H)

Example 452

(2S)-N-Hydroxy-2-[5-{3-(((2S)-2-(aminobutyl) amino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (105 mg) from L-Boc-Abu-OH

NMR (DMSO-d₆, δ): 0.98 (3H, t, J=6.5Hz), 1.74-2.06 (4H, m), 1.89 (2H, qt, J=6.5, 6.5Hz), 2.36-2.45 (1H, m), 2.96-3.27 (4H, m), 3.44-3.54 (1H, m), 3.90 (1H, br), 7.22 (1H, d, J=4.0Hz), 7.39-7.46 (3H, m), 7.52-7.56 (1H, m), 7.91 (1H, s), 8.32 (2H, br), 8.85 (1H, s), 10.56 (1H, s), 10.60 (1H, s)

MS (ESI+): 467.2 (M+H)

Example 453

(2S)-N-Hydroxy-2-[5-{3-(2-(piperizinocarbonyloxy)-acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-

thiopyran-2-acetamide 1,1-dioxide (47 mg)

NMR (DMSO-d₆, δ): 1.48-1.58 (6H, m), 1.75-2.05 (4H, m),
2.37-2.46 (1H, m), 2.95-3.26 (4H, m), 3.46-3.55
(5H, m), 4.62 (2H, s), 7.20 (1H, d, J=4.0Hz),
5 7.35-7.38 (3H, m), 7.62 (1H, d, J=4.0Hz), 8.00 (1H,
s), 10.17 (1H, s), 10.60 (1H, s)
MS (ESI-): 548.2 (M-H)

Example 454

10 (2S)-N-Hydroxy-2-[5-{3-(2-(benzylaminocarbonyloxy)-
acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (55 mg)

NMR (DMSO-d₆, δ): 1.73-2.05 (4H, m), 2.37-2.46 (1H, m),
2.94-3.26 (4H, m), 3.42-3.53 (1H, m), 4.22 (2H, d,
15 J=5.0Hz), 4.61 (2H, s), 7.20-7.48 (10H, m), 7.93-
7.97 (2H, m), 8.84 (1H, br), 10.15 (1H, s), 10.60
(1H, s)
MS (ESI-): 570.1 (M-H)

20 Example 455

(2S)-N-Hydroxy-2-[5-{3-(2-(3-methylphenoxy)-
acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (30 mg)

NMR (DMSO-d₆, δ): 1.73-2.06 (4H, m), 2.30 (3H, s),
25 2.37-2.47 (1H, m), 2.95-3.26 (4H, m), 3.40-3.50
(1H, m), 4.70 (2H, s), 6.70-6.75 (3H, m), 7.20-
7.22 (2H, m), 7.38-7.40 (2H, m), 7.43 (1H, d,
J=4.0Hz), 7.56 (1H, d, J=7.0Hz), 8.03 (1H, s),
8.84 (1H, s), 10.17 (1H, s), 10.60 (1H, s)
30 MS (ESI+): 565.2 (M+H+Cl)

Example 456

(2S)-N-Hydroxy-2-[5-{3-(2-(3-pyridyloxy)-
acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-
35 thiopyran-2-acetamide 1,1-dioxide (50 mg)

NMR (DMSO-d₆, δ): 1.72-2.06 (4H, m), 2.37-2.48 (1H, m),
2.96-3.27 (4H, m), 3.40-3.50 (1H, m), 4.90 (2H, s),
7.20 (1H, d, J=4.0Hz), 7.35-7.42 (3H, m), 7.52-
7.56 (2H, m), 7.64-7.66 (1H, m), 8.00 (1H, s),
8.30 (1H, d, J=4.5Hz), 8.50 (1H, d, J=2.0Hz),
10.30 (1H, s), 10.60 (1H, s)
MS (ESI-): 514.1 (M-H)

Example 457

(2S)-N-Hydroxy-2-[5-{3-(2-(4-pyridyloxy)acetylamino)-
phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (35 mg)
NMR (DMSO-d₆, δ): 1.72-2.05 (4H, m), 2.35-2.44 (1H, m),
2.95-3.25 (4H, m), 3.42-3.53 (1H, m), 5.26 (2H, s),
7.07 (2H, d, J=7.0Hz), 7.20 (1H, d, J=4.0Hz),
7.40-7.42 (4H, m), 8.03 (1H, s), 8.41 (2H, d,
J=7.0Hz)
MS (ESI+): 516.1 (M+H)

Example 458

(2S)-N-Hydroxy-2-[5-{3-(((2S)-2-amino-3-(4-pyridyl)-
propionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (160 mg) L-Boc4-PyAla-OH
NMR (DMSO-d₆, δ): 1.72-2.06 (4H, m), 2.35-2.46 (1H, m),
2.96-3.39 (6H, m), 3.44-3.55 (1H, m), 4.30 (1H,
br), 7.22 (1H, d, J=4.0Hz), 7.42-7.48 (4H, m),
7.55 (1H, d, J=6.0Hz), 7.85 (1H, s), 8.39 (2H, br),
8.70 (2H, d, J=5.5Hz), 10.60 (1H, s), 10.62 (1H,
s)
MS (ESI+): 529.2 (M+H)

Example 459

(2S)-N-Hydroxy-2-[5-{3-(((2S)-2-amino-3-
phenylpropionyl)amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-
2H-thiopyran-2-acetamide 1,1-dioxide (40 mg) from

L-Boc-Phe-OH

5 NMR (DMSO-d₆, δ): 1.74-2.06 (4H, m), 2.35-2.44 (1H, m),
2.95-3.27 (6H, m), 3.43-3.53 (1H, m), 4.15 (1H,
br), 7.22 (1H, d, J=4.0Hz), 7.25-7.35 (5H, m),
7.39-7.46 (4H, m), 7.80 (1H, s), 8.32 (2H, br),
8.85 (1H, br), 10.47 (1H, s), 10.73 (1H, s)
MS (ESI+): 528.3 (M+H)

10 The following compounds were obtained in a similar
manner to that of Example 130.

Example 460

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(methanesulfonylamino)acetylamino)phenyl)-2-thienyl]-
15 3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (75
mg)

20 NMR (DMSO-d₆, δ): 1.46-1.72 (8H, m), 1.87-1.99 (2H, m),
2.06-2.24 (2H, m), 2.81-2.92 (2H, m), 3.02 (3H, s),
3.05-3.21 (2H, m), 3.28-3.52 (1H, m), 3.68-3.80
(1H, m), 3.98-4.06 (2H, m), 4.53, 4.87 (1H, br s),
5.94-6.08 (1H, m), 7.06-7.21 (4H, m), 7.42-7.52
(2H, m), 8.58, 8.59 (1H, br s)

MS (ESI-): 598 (M-H)

25 Example 461

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(phenylacetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (132 mg)

30 NMR (CDCl₃, δ): 1.30-1.73 (8H, m), 1.84-1.97 (2H, m),
2.04-2.23 (2H, m), 2.70-2.90 (2H, m), 2.97-3.16
(2H, m), 3.26-3.51 (1H, m), 3.63-3.73 (1H, m),
3.73 (2H, s), 4.52, 4.72 (1H, br s), 7.08-7.62
(12H, m), 8.68 (1H, br s)

MS (ESI-): 580 (M-H)

Example 462

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(cyclopropanecarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (550 mg)

5 NMR (DMSO-d₆, δ): 0.72-0.89 (4H, m), 1.32-1.64 (6H, m),
1.67-2.06 (5H, m), 2.34-2.49 (1H, m), 2.87-3.30
(5H, m), 3.41-3.53 (1H, m), 3.72-3.91 (1H, m),
4.44, 4.75 (1H, s), 7.16-7.26 (1H, m), 7.39-7.52
(4H, m), 8.02 (1H, s)

10 MS (ESI-): 531 (M-H)

Example 463

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(propoxy-carbonylamino)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (93 mg)

15 NMR (CDCl₃, δ): 0.93-0.99 (3H, m), 1.44 (2H, br),
1.65-1.75 (6H, m), 1.95 (2H, br), 2.04-2.26 (2H,
m), 2.72-2.92 (2H, m), 3.01-3.15 (4H, m), 3.28-
3.48 (1H, m), 3.70 (1H, br), 3.95-4.12 (4H, m),
20 4.53 (1/2H, s), 4.84 (1/2H, s), 5.54-5.64 (1H, m),
7.12-7.23 (4H, m), 7.50 (1H, br s), 7.58 (1H, s),
8.28 (1H, br), 8.70-8.78 (1H, m)

MS (ESI-): 606.1 (M-H)

25 Example 464

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(cyclopentylloxycarbonylamino)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (53 mg)

30 NMR (CDCl₃, δ): 1.44 (4H, br), 1.60-1.74 (4H, m),
1.86-1.96 (6H, m), 2.05-2.24 (2H, m), 2.70-2.89
(2H, m), 2.96-3.20 (4H, m), 3.29-3.52 (1H, m),
3.64-3.75 (1H, m), 3.94-4.02 (2H, m), 4.54 (1/2H,
s), 4.83 (1/2H, s), 5.16 (1H, br), 5.45-5.54 (1H,
35 m), 7.16-7.25 (3H, m), 7.51-7.60 (2H, m), 8.30 (1H,

br)

MS (ESI-): 632.1 (M-H)

The following compounds were obtained in a similar
5 manner to that of Example 211.

Example 465

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2-(2-
oxopyrrolidinyl)acetyl amino)phenyl)-2-thienyl]-3,4,5,6-
10 tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (520 mg)

NMR (DMSO-d₆, δ): 1.32-1.63 (6H, m), 1.68-2.09 (6H, m),
2.28 (2H, t, J=7Hz), 2.35-2.48 (1H, m), 2.86-3.53
(6H, m), 3.46 (2H, t, J=7Hz), 3.22-3.40 (1H, m),
4.05 (2H, s), 4.44, 4.75 (1H, s), 7.16-7.25 (1H,
15 m), 7.32-7.46 (4H, m), 8.02 (1H, s), 10.20 (1H, s),
11.25 (1H, s)

MS (ESI-): 588 (M-H)

Example 466

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(((3S)-N-tert-
butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-
carbonyl)amino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (135 mg)

NMR (DMSO-d₆, δ): 1.18-2.06 (10H, m), 1.31 (9H, s),
25 2.34-2.47 (1H, m), 2.88-3.31 (7H, m), 3.38-3.54
(1H, m), 3.72-3.88 (1H, m), 4.36-4.85 (4H, m),
7.14-7.50 (9H, m), 7.88-8.00 (1H, m), 10.16 (1H,
s), 11.24 (1H, s)

MS (ESI-): 722 (M-H)

Example 467

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(oxolane-2-
carbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (670 mg)

35 NMR (DMSO-d₆, δ): 1.38-1.62 (6H, m), 1.70-2.08 (7H, m),

2.14-2.78 (1H, m), 2.36-2.50 (1H, m), 2.90-3.32
(5H, m), 3.40-3.53 (1H, m), 3.74-3.90 (1H, dd,
J=7Hz), 4.02 (1H, dd, J=7Hz), 4.42 (1H, dd, J=7Hz),
4.45, 4.75 (1H, s), 7.19-7.25 (1H, m), 7.31-7.44
5 (3H, m), 7.65 (1H, d, J=8Hz), 8.07 (1H, s), 9.78
(1H, s), 11.25 (1H, s)

MS (ESI-): 561 (M-H)

Example 468

10 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(oxolane-3-
carbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (700 mg)

NMR (DMSO-d₆, δ): 1.33-1.63 (6H, m), 1.69-2.15 (4H, m),
2.09 (2H, dd, J=8Hz), 2.35-2.48 (1H, m), 2.86-3.32
15 (4H, m), 3.39-3.56 (1H, m), 3.65-3.86 (4H, m),
3.88-4.00 (1H, m), 4.45, 4.75 (1H, s), 7.18-7.25
(1H, m), 7.30-7.52 (4H, m), 8.02 (1H, s), 10.15
(1H, s), 11.24, 11.25 (1H, s)

MS (ESI-): 561 (M-H)

Example 469

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(ethyl-
aminocarbonylamino)acetyl amino)phenyl}-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (4.7 g)

25 NMR (CDCl₃, δ): 0.85-0.93 (3H, m), 1.45 (4H, br),
1.55-1.68 (2H, m), 1.92 (2H, br), 2.01-2.25 (2H,
m), 2.92-3.10 (7H, m), 3.26-3.75 (1H, m), 3.44-
3.54 (2H, m), 3.68-4.02 (2H, m), 4.30-4.40 (1H, m),
4.65 (1/2H, br), 4.92 (1/2H, br), 6.02 (1H, br),
30 7.07-7.26 (7H, m), 7.54 (1/2H, s), 7.60 (1/2H, s),
9.27 (1/2H, s), 9.32 (1/2H, s)

MS (ESI-): 591.2 (M-H)

Example 470

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-

isovalerylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (200 mg)

5 NMR (CDCl₃, δ): 1.04 (6H, d, J=6.0Hz), 1.16 (2H, d, J=7.5Hz), 1.45 (2H, br), 1.65-1.75 (2H, m), 1.92-1.95 (2H, m), 2.07-2.30 (2H, m), 2.28 (2H, br), 2.30-2.40 (1H, m), 2.71-2.90 (2H, m), 3.04-3.15 (4H, m), 3.30-3.50 (1H, m), 3.64-3.75 (1H, m), 4.52 (1/2H, br s), 4.82 (1/2H, br s), 7.20-7.30 (3H, m), 7.39-7.46 (1H, m), 7.50-7.57 (2H, m), 10 7.62-7.66 (1H, m), 8.37-8.47 (1H, m)

MS (ESI-): 547.1 (M-H)

Example 471

15 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(methoxyacetyl amino)acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (195 mg)

20 NMR (CDCl₃, δ): 1.45 (2H, br), 1.67 (4H, br), 1.97 (2H, br), 2.07-2.24 (2H, m), 2.80-2.87 (2H, m), 3.01-3.06 (1H, m), 3.11-3.20 (3H, m), 3.30-3.44 (1H, m), 3.46 (3H, s), 3.68-3.78 (1H, m), 4.04 (2H, s), 4.09-4.13 (1H, m), 4.25-4.32 (1H, m), 4.53 (1/2H, s), 4.84 (1/2H, s), 7.08-7.24 (3H, m), 7.42 (2H, br), 7.48-7.54 (2H, m), 8.56 (1H, br), 9.08 (1/2H, s), 9.18 (1/2H, br s)

25 MS (ESI+): 591.1 (M+H)

Example 472

30 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(3-pyridylcarbonyl amino)acetyl amino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (90 mg)

35 NMR (CDCl₃, δ): 1.36 (2H, br), 1.65 (4H, br), 1.94 (2H, br), 2.06-2.23 (2H, m), 2.80-3.20 (7H, m), 3.55-3.72 (1H, m), 4.36 (1/2H, br s), 4.37-4.65 (2H, m), 4.86 (1/2H, s), 7.13-7.30 (5H, m), 7.43-7.49 (1H, m), 7.54 (1H, br s), 7.75-7.81 (1H, m), 8.23 (1H,

d, J=7.5Hz), 8.76 (1H, br), 9.27 (1/2H, s), 9.31-9.34 (1H, m), 9.40 (1/2H, s)

MS (ESI+): 625.1 (M+H)

5 Example 473

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(methoxymethylaminocarbonylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg) was obtained in a similar manner to that of Example 348.

10 NMR (CDCl₃, δ): 1.25 (2H, br), 1.43 (2H, br), 1.64 (2H, br), 1.93 (2H, br), 2.05-2.22 (2H, m), 2.70-2.88 (2H, m), 3.00-3.13 (4H, m), 3.37 (3H, s), 3.45-3.52 (4H, m), 4.55 (1/2H, br), 4.81 (1/2H, br), 5.40-5.49 (1H, m), 7.08-7.20 (6H, m), 7.27-7.40 (1H, m), 8.91 (1/2H, br), 8.98 (1/2H, br)

15 MS (ESI-): 567.1 (M-H+NH₃)

Example 474

20 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(3-pyridylmethylamino)acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (100 mg) was obtained in a similar manner to that of Example 249.

NMR (CDCl₃, δ): 1.42 (2H, br), 1.63-1.68 (4H, m), 1.95 (2H, br), 2.07-2.23 (2H, m), 2.68-2.95 (2H, m), 3.08 (2H, br s), 3.13 (2H, br), 3.27-3.44 (1H, m), 3.46 (2H, s), 3.62-3.70 (1H, m), 3.90 (2H, s), 4.52 (1/2H, br), 4.82 (1/2H, br), 7.24-7.34 (6H, m), 7.53-7.57 (1H, m), 7.65-7.70 (2H, m), 8.57 (1H, d, J=5.0Hz), 8.62 (1/2H, br), 8.65 (1H, s), 8.90 (1/2H, s), 9.17 (1H, d, J=6.0Hz)

30 MS (ESI+): 613.2 (M+H)

Example 475

35 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-{3-(2-(tert-butylamino)acetylamino)phenyl}-2-thienyl]-3,4,5,6-

tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (95 mg) was obtained in a similar manner to that of Example 249.

NMR (CDCl₃, δ): 1.17 (9H, s), 1.46 (2H, br), 1.65-1.70 (4H, m), 1.96 (2H, br), 2.09-2.23 (2H, m), 2.64-2.86 (2H, m), 3.06 (2H, br s), 3.10-3.15 (2H, m), 3.36 (2H, br s), 3.43-3.70 (2H, m), 4.53 (1/2H, br), 4.80 (1/2H, br), 7.22-7.34 (5H, m), 7.56-7.60 (1H, m), 7.78 (1H, s), 9.53 (1H, s)

MS (ESI-): 593.6 (M-H+NH₃)

The following compounds were obtained in a similar manner to that of Example 54.

Example 476

(2S)-N-Hydroxy-2-[5-(3-(2-(N-methanesulfonylamino)-acetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (32 mg)

NMR (DMSO-d₆, δ): 1.72-2.08 (4H, m), 2.33-2.48 (1H, m), 2.92-3.56 (7H, m), 3.00 (3H, s), 3.87 (1H, d, J=7Hz), 7.21 (1H, d, J=3Hz), 7.34-7.52 (4H, m), 7.96 (1H, s), 8.84 (1H, s)

MS (ESI-): 514 (M-H)

Example 477

(2S)-N-Hydroxy-2-[5-(3-phenylacetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (92 mg)

NMR (DMSO-d₆, δ): 1.67-2.08 (4H, m), 2.32-2.51 (1H, m), 2.89-3.54 (5H, m), 3.66 (2H, s), 7.17-7.53 (11H, m), 8.00 (1H, s), 10.30 (1H, s), 10.60 (1H, s)

MS (ESI-): 497 (M-H)

Example 478

(2S)-N-Hydroxy-2-[5-(3-(2-(2-oxopyrrolidinyl)-acetylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-

thiopyran-2-acetamide 1,1-dioxide (420 mg)

NMR (DMSO-d₆, δ): 1.68-2.12 (6H, m), 2.19-2.48 (3H, m),
2.90-3.61 (7H, m), 4.06 (2H, s), 7.20 (1H, d,
J=3Hz), 7.31-7.52 (5H, m), 8.02 (1H, s), 10.23 (1H,
s), 10.62 (1H, s)

MS (ESI-): 504 (M-H)

Example 479

(2S)-N-Hydroxy-2-[5-(3-(((3S)-1,2,3,4-tetrahydro-
isolquinoline-3-carbonyl)amino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide
hydrochloride (88 mg) from (2S)-N-(2-tetrahydropyranyloxy-2-
[5-(3-(((3S)-N-tert-butoxycarbonyl-1,2,3,4-
tetrahydroisoquinoline-3-carbonyl)amino)phenyl)-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide

NMR (DMSO-d₆, δ): 1.66-2.14 (4H, m), 2.32-2.48 (1H, m),
2.86-3.92 (7H, m), 4.26-4.51 (3H, m), 7.12-7.52
(8H, m), 7.56-7.68 (1H, m), 8.03 (1H, s), 9.55 (1H,
br s), 9.96 (1H, br s), 10.67 (1H, s), 11.22 (1H,
s)

MS (ESI+): 540 (M+H)

Example 480

(2S)-N-Hydroxy-2-[5-(3-(cyclopropanecarbonylamino)-
phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-
acetamide 1,1-dioxide (410 mg)

NMR (DMSO-d₆, δ): 0.70-0.90 (4H, m), 1.66-2.10 (5H, m),
2.34-2.49 (1H, m), 3.42-3.55 (1H, m), 7.21 (1H, d,
J=3Hz), 7.28-7.39 (2H, m), 7.40 (1H, d, J=3Hz),
7.42-7.52 (1H, m), 8.01 (1H, s), 10.33 (1H, s),
10.61 (1H, s)

MS (ESI-): 447 (M-H)

Example 481

(2S)-N-Hydroxy-2-[5-(3-(oxolane-2-carbonylamino)-

phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (340 mg)

5 NMR (DMSO-d₆, δ): 1.71-2.07 (7H, m), 2.14-2.27 (1H, m),
2.93-3.27 (4H, m), 3.40-3.55 (1H, m), 3.84 (1H, dd,
J=7Hz), 4.00 (1H, dd, J=7Hz), 4.41 (1H, d, J=7Hz),
7.21 (1H, d, J=3Hz), 7.32-7.44 (3H, m), 7.65 (1H,
d, J=8Hz), 8.07 (1H, s), 8.85 (1H, s), 9.78 (1H,
s), 10.60 (1H, s)

MS (ESI-): 477 (M-H)

10 Example 482

(2S)-N-Hydroxy-2-[5-(3-(oxolane-3-carbonylamino)-phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (541 mg)

15 NMR (DMSO-d₆, δ): 1.68-2.20 (4H, m), 2.09 (2H, dd,
J=8Hz), 2.24-2.49 (1H, m), 2.92-3.31 (4H, m),
3.43-3.54 (1H, m), 3.65-3.76 (4H, m), 3.95 (1H, t,
J=8Hz), 7.21 (1H, d, J=3Hz), 7.30-7.54 (4H, m),
8.02 (1H, s), 10.17 (1H, s), 10.61 (1H, s)

20 MS (ESI-): 477 (M-H)

Example 483

(2S)-N-Hydroxy-2-[5-(3-(2-(ethylaminocarbonylamino)-acetylaminophenyl)-2-thienyl)-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.0 mg)

25 NMR (DMSO-d₆, δ): 1.00 (3H, t, J=7.5Hz), 1.73-2.05 (4H,
m), 2.38-2.46 (1H, m), 2.95-3.25 (6H, m), 3.43-
3.53 (1H, m), 3.83 (2H, d, J=6.0Hz), 6.10-6.18 (2H,
m), 7.20 (1H, d, J=4.0Hz), 7.35-7.37 (2H, m), 7.40
30 (1H, d, J=4.0Hz), 7.46-7.50 (1H, m), 7.97 (1H, s),
8.84 (1H, s)

MS (ESI-): 507.2 (M-H)

Example 484

35 (2S)-N-Hydroxy-2-[5-(3-isovalerylaminophenyl)-2-

thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (120 mg)

5 NMR (DMSO-d₆, δ): 0.95 (6H, d, J=7.5Hz), 1.74-2.15 (5H, m), 2.20 (2H, d, J=7.0Hz), 2.38-2.45 (1H, m), 2.95-3.26 (4H, m), 3.40-3.53 (1H, m), 7.20 (1H, d, J=4.0Hz), 7.32-7.37 (2H, m), 7.46-7.50 (1H, m), 8.00 (1H, s), 9.97 (1H, s), 10.60 (1H, s)

MS (ESI-): 463.0 (M-H)

10 Example 485

(2S)-N-Hydroxy-2-[5-(3-(methoxymethylaminocarbonylamino)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

15 NMR (DMSO-d₆, δ): 1.73-2.04 (4H, m), 2.35-2.45 (1H, m), 2.95-3.28 (6H, m), 3.26 (3H, s), 3.37-3.42 (1H, m), 6.24 (1H, t, J=7.0Hz), 7.16-7.27 (4H, m), 7.37 (1H, d, J=4.0Hz), 7.83 (1H, s), 8.67 (1H, s)

MS (ESI-): 466.4 (M-H)

20 Example 486

(2S)-N-Hydroxy-2-[5-{3-(2-(3-pyridylmethylamino)-acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (60 mg)

25 NMR (DMSO-d₆, δ): 1.72-2.06 (4H, m), 2.35-2.45 (1H, m), 2.97-3.28 (4H, m), 3.42-3.50 (1H, m), 3.98 (2H, br), 4.35 (2H, br), 7.22 (1H, d, J=4.0Hz), 7.38-7.43 (2H, m), 7.48-7.52 (1H, m), 7.68-7.73 (1H, m), 7.93 (1H, s), 8.23 (1H, d, J=7.0Hz), 8.74 (1H, d, J=6.0Hz), 8.85 (1H, s), 9.68 (1H, br)

30 MS (ESI-): 527.1 (M-H)

Example 487

35 (2S)-N-Hydroxy-2-[5-{3-(2-(propoxycarbonylamino)-acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

NMR (DMSO-d₆, δ): 0.91 (3H, t, J=7.0Hz), 1.58 (2H, qt, J=7.0, 7.0Hz), 1.73-2.05 (4H, m), 2.37-2.48 (1H, m), 2.94-3.27 (4H, m), 3.44-3.53 (1H, m), 3.79 (2H, d, J=6.0Hz), 3.93 (2H, t, J=7.0Hz), 7.21 (1H, d, J=4.0Hz), 7.35-7.42 (4H, m), 7.45-7.48 (1H, m), 7.97 (1H, s), 8.84 (1H, s), 10.08 (1H, s), 10.61 (1H, s)

MS (ESI-): 522.1 (M-H)

10 Example 488

(2S)-N-Hydroxy-2-[5-{3-(2-(cyclopentyloxycarbonylamino)acetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (30 mg)

NMR (DMSO-d₆, δ): 1.50-1.70 (6H, m), 1.75-2.05 (6H, m), 2.37-2.48 (1H, m), 2.95-3.25 (4H, m), 3.43-3.53 (1H, m), 3.77 (2H, d, J=5.0Hz), 4.97 (1H, br), 7.20 (1H, d, J=4.0Hz), 7.30 (1H, t, J=7.0Hz), 7.35-7.38 (2H, m), 7.41 (1H, d, J=4.0Hz), 7.45-7.48 (1H, m), 7.98 (1H, s), 8.83 (1H, br), 10.07 (1H, s), 10.60 (1H, br)

MS (ESI-): 548.1 (M-H)

Example 489

(2S)-N-Hydroxy-2-[5-{3-(2-(methoxyacetylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (70 mg)

NMR (DMSO-d₆, δ): 1.74-2.05 (4H, m), 2.36-2.48 (1H, m), 2.95-3.26 (4H, m), 3.37 (3H, s), 3.43-3.54 (1H, m), 3.39 (2H, s), 3.45 (2H, d, J=6.0Hz), 7.20 (1H, d, J=4.0Hz), 7.36-7.40 (2H, m), 7.42 (1H, d, J=4.0Hz), 7.43-7.48 (1H, m), 7.94 (1H, s), 8.05 (1H, t, J=6.0Hz), 8.84 (1H, s), 10.13 (1H, s), 10.60 (1H, s)

MS (ESI-): 508.1 (M-H)

Example 490

(2S)-N-Hydroxy-2-[5-{3-(2-(tert-butylamino)-acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (50 mg)

5 NMR (DMSO-d₆, δ): 1.32 (9H, s), 1.72-2.06 (4H, m),
2.35-2.46 (1H, m), 2.96-3.28 (4H, m), 3.38-3.52
(1H, m), 3.96 (2H, t, J=7.0Hz), 7.22 (1H, d,
J=4.0Hz), 7.41-7.44 (3H, m), 7.51-7.54 (1H, m),
7.97 (1H, s), 8.84 (1H, br), 8.95-8.98 (2H, br)

10 MS (ESI+): 494.1 (M+H)

Example 491

(2S)-N-Hydroxy-2-[5-{3-(2-(3-pyridylcarbonylamino)-acetylamino)phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (60 mg)

15 NMR (DMSO-d₆, δ): 1.72-2.04 (4H, m), 2.37-2.45 (1H,
m), 2.95-3.25 (4H, m), 3.40-3.52 (1H, m), 4.00-
4.06 (2H, br), 4.13 (2H, d, J=7.0Hz), 7.20 (1H, d,
J=4.0Hz), 7.32-7.39 (2H, m), 7.42 (1H, d, J=4.0Hz),
20 7.46-7.50 (1H, m), 7.59-7.64 (1H, m), 8.02 (1H, s),
8.30-8.33 (1H, m), 8.77 (1H, d, J=6.0Hz), 9.10 (1H,
s), 9.15 (1H, t, J=7.5Hz)

MS (ESI-): 527.3 (M-H)

Example 492

(2S)-N-Hydroxy-2-[5-{3-(3,3-dimethylbutyrylamino)-phenyl}-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg) was obtained from 3,3-dimethylbutyric acid in a similar manner to that of Example
30 408.

NMR (DMSO-d₆, δ): 1.03 (9H, s), 1.66-2.10 (4H, m), 2.21
(2H, s), 2.34-2.48 (1H, m), 2.92-3.29 (4H, m),
3.42-3.56 (1H, m), 7.20 (1H, d, J=3Hz), 7.28-7.38
(2H, m), 7.40 (1H, d, J=3Hz), 7.45-7.54 (1H, m),
35 7.99 (1H, s), 9.93 (1H, s), 10.61 (1H, s)

MS (ESI-): 477 (M-H)

Example 493

(2S)-N-Hydroxy-2-[5-(4-ethoxyphenyl)-2-thienyl]-
3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (8.5
mg) was obtained in a similar manner to that of Example 168.

NMR (DMSO-d₆, δ): 1.35 (3H, t, J=7.0Hz), 1.73-2.04 (4H,
m), 2.34-2.44 (1H, m), 2.95-3.25 (4H, m), 3.62-
3.68 (1H, m), 4.06 (2H, q, J=7.0Hz), 6.97 (2H, d,
J=7.5Hz), 7.16 (1H, d, J=4.0Hz), 7.33 (1H, d,
J=4.0Hz), 7.56 (1H, d, J=7.5Hz)

MS (ESI+): 410.2 (M+H)

The following compounds were obtained in a similar
manner to that of Example 130.

Example 494

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
(cyclobutylcarbonylamino)phenyl)-2-thienyl]-3,4,5,6-
tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (340 mg)

NMR (DMSO-d₆, δ): 1.37-1.65 (6H, m), 1.70-2.30 (10H, m),
2.37-2.46 (1H, m), 2.90-3.55 (7H, m), 3.75-3.89
(1H, m), 4.44, 4.75 (1H, s), 7.19-7.22 (1H, m),
7.34-7.40 (3H, m), 7.45-7.51 (1H, m), 8.03 (1H, s),
9.83 (1H, s)

Example 495

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-
(isobutylaminophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-
thiopyran-2-acetamide 1,1-dioxide (330 mg)

NMR (DMSO-d₆, δ): 1.11 (6H, d, J=7.0Hz), 1.36-1.64 (6H,
m), 1.70-2.05 (4H, m), 2.35-2.45 (1H, m), 2.55-
2.64 (1H, m), 2.90-3.54 (6H, m), 3.75-3.90 (1H, m),
4.45, 4.75 (1H, s), 7.20-7.23 (1H, m), 7.33-7.41
(3H, m), 7.45-7.51 (1H, m), 8.03 (1H, s)

Example 496

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-(2,2-dimethylpropionylamino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (267 mg)

NMR (DMSO-d₆, δ): 1.24 (9H, s), 1.36-1.64 (6H, m), 1.69-2.09 (4H, m), 2.36-2.53 (1H, m), 2.88-3.29 (4H, m), 3.30-3.51 (2H, m), 3.74-3.91 (1H, m), 4.44 (0.5H, s), 4.76 (0.5H, s), 7.19-7.24 (1H, m), 7.30-7.42 (3H, m), 7.59-7.65 (1H, m), 8.01 (1H, s), 9.30 (1H, s)

MS (ESI-): 547 (M-H)

Example 497

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(3-((E)-2-butenoylamino)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (160 mg)

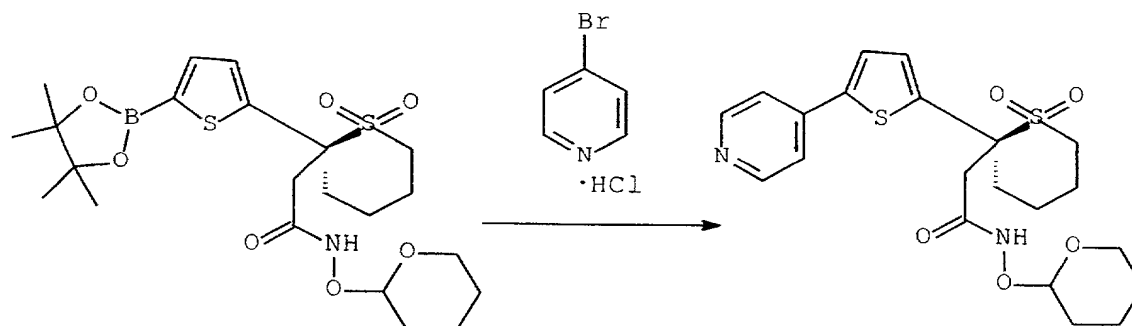
NMR (CDCl₃, δ): 1.37-1.76 (6H, m), 1.86-2.02 (5H, m), 2.04-2.26 (2H, m), 2.68-2.94 (2H, m), 3.00-3.19 (4H, m), 3.30-3.51 (1H, m), 3.62-3.76 (1H, m), 4.55 (0.5H, s), 4.83 (0.5H, s), 6.00 (1H, dd, J=1.5, 15Hz), 6.94-7.09 (1H, m), 7.13-7.33 (4H, m), 7.49-7.67 (3H, m), 8.45-8.55 (1H, m)

MS (ESI-): 531 (M-H)

The following compounds were obtained in a similar manner to that of Example 201.

Example 498

5



20 (2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-pyridyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (60 mg)

NMR (CDCl₃, δ): 1.40-1.76 (6H, m), 1.86-2.00 (2H, m),
 2.06-2.25 (2H, m), 2.71-2.93 (2H, m), 3.00-3.19
 25 (4H, m), 3.25-3.55 (1H, m), 3.60-3.799 (1H, m),
 4.50 (0.5H, s), 4.84 (0.5H, s), 7.16-7.35 (1H, m),
 7.44-7.49 (3H, m), 8.21 (0.5H, s), 8.28 (0.5H, s),
 8.59 (2H, d, J=8Hz)

MS (ESI⁺): 451 (M+H)

30

Example 499

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-(methylaminocarbonylmethyl)phenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (67 mg)

35 MS (ESI⁻): 519 (M-H)

Example 500

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(2-(methylaminocarbonyl)-5-benzofuranyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (283 mg)

40 NMR (CDCl₃, δ): 1.38-1.76 (6H, m), 1.88-2.02 (2H, m),
 2.04-2.25 (2H, m), 2.65-2.93 (2H, m), 3.01-3.18

(7H, m), 3.26-3.51 (1H, m), 3.60-3.74 (1H, m),
4.55 (0.5H, s), 4.83 (0.5H, s), 6.61-6.71 (1H, m),
7.21-7.31 (2H, m), 7.43-7.50 (2H, m), 7.60-7.66
(1H, m), 7.83-7.88 (1H, m), 8.20 (0.5H, s), 8.27
(0.5H, s)

Example 501

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-methylthiophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (129 mg) was obtained in a similar manner to that of Example 89.

NMR (CDCl₃, δ): 1.38-1.76 (6H, m), 1.86-2.00 (2H, m),
2.05-2.24 (2H, m), 2.51 (3H, s), 2.61-2.90 (2H, m),
3.03-3.17 (4H, m), 3.26-3.50 (1H, m), 3.56-3.70
(1H, m), 4.52 (0.5H, s), 4.79 (0.5H, s), 7.20-7.36
(3H, m), 7.45-7.54 (2H, m), 7.62-7.68 (1H, m),
7.98 (0.5H, s), 8.09-8.15 (0.5H, m)

Example 502

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-(4-methanesulfonyl)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (57 mg) was obtained from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-methylthiophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide in a similar manner to that of Preparation 1-4).

NMR (CDCl₃, δ): 1.40-1.59 (4H, m), 1.62-1.74 (2H, m),
1.88-2.02 (2H, m), 2.05-2.25 (2H, m), 2.76-2.88
(2H, m), 3.04-3.20 (7H, m), 3.40-3.54 (1H, m),
3.60-3.77 (1H, m), 4.54 (0.5H, s), 4.82 (0.5H, s),
7.26-7.35 (1H, m), 7.37-7.43 (1H, m), 7.73-7.80
(2H, m), 7.90-7.97 (2H, m), 8.14 (0.5H, s), 8.20
(0.5H, s)

The following compounds were obtained in a similar manner to that of Example 54.

Example 503

(2S)-N-Hydroxy-2-[5-(4-methanesulfonyl)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (27 mg)

NMR (DMSO-d₆, δ): 1.72-2.10 (4H, m), 2.36-2.55 (1H, m), 2.96-3.08 (2H, m), 3.12-3.36 (5H, m), 3.39-3.56 (1H, m), 7.28 (1H, d, J=3.9Hz), 7.70 (1H, d, J=3.9Hz), 7.91 (2H, d, J=8Hz), 7.96 (2H, d, J=8Hz), 8.86 (1H, s)

MS (ESI-): 442 (M-H)

Example 504

(2S)-N-Hydroxy-2-[5-(4-methylaminocarbonylmethyl)-phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (25 mg)

NMR (DMSO-d₆, δ): 1.70-2.06 (4H, m), 2.34-2.52 (1H, m), 2.59 (3H, d, J=4.5Hz), 2.95-3.34 (4H, m), 3.36-3.54 (3H, m), 7.20 (1H, d, J=3.9Hz), 7.29 (2H, d, J=8Hz), 7.43 (1H, d, J=3.9Hz), 7.56 (1H, d, J=8Hz), 7.94-8.02 (1H, m), 8.85 (1H, s)

MS (ESI-): 435 (M-H)

Example 505

(2S)-N-Hydroxy-2-[5-(4-pyridyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (3.1 mg)

MS (ESI+): 367 (M-H)

Example 506

(2S)-N-Hydroxy-2-[5-(2-(methylaminocarbonyl)-5-benzofuranyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide hydrochloride (119 mg)

NMR (DMSO-d₆, δ): 1.72-2.10 (4H, m), 2.36-2.56 (1H, m), 2.81 (3H, d, J=4.8Hz), 2.95-3.31 (4H, m), 3.40-3.55 (1H, m), 7.22 (1H, d, J=3.9Hz), 7.49 (1H, d,

J=3.9Hz), 7.53 (1H, s), 7.69 (1H, d, J=8Hz), 7.75 (1H, d, J=8Hz), 8.03 (1H, s), 8.73 (1H, q, J=4.8Hz), 8.86 (1H, br s), 10.60 (1H, br s)

MS (ESI-): 461 (M-H)

5

Example 507

(2S)-N-(2-Tetrahydropyranyloxy)-2-[5-[4-(methanesulfinyl)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (45 mg) was obtained from (2S)-N-(2-tetrahydropyranyloxy)-2-[5-(4-methylthiophenyl)-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide in a similar manner to that of Preparation 1-4).

NMR (CDCl₃, δ): 1.38-1.76 (6H, m), 1.84-2.01 (2H, m), 2.05-2.25 (2H, m), 2.77 (3H, s), 2.77-2.88 (2H, m), 3.00-3.18 (4H, m), 3.30-3.54 (1H, m), 3.64-3.79 (1H, m), 4.53 (0.5H, s), 4.83 (0.5H, s), 7.25-7.34 (2H, m), 7.65 (2H, d, J=8Hz), 7.70-7.78 (2H, m), 8.66 (0.5H, s), 8.71 (0.5H, s)

MS (ESI-): 510 (M-H)

Example 508

(2S)-N-Hydroxy-2-[5-[4-(methanesulfinyl)phenyl]-2-thienyl]-3,4,5,6-tetrahydro-2H-thiopyran-2-acetamide 1,1-dioxide (11 mg) was obtained in a similar manner to that of Example 54.

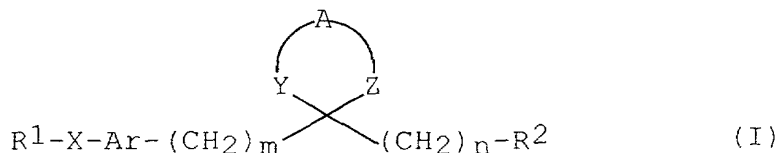
NMR (DMSO-d₆, δ): 1.71-2.10 (4H, m), 2.35-2.55 (1H, m), 2.78 (3H, s), 2.95-3.08 (2H, m), 3.11-3.38 (2H, m), 3.41-3.55 (1H, m), 7.25 (1H, d, J=3.9Hz), 7.61 (1H, d, J=3.9Hz), 7.72 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz), 8.85 (1H, s)

MS (ESI-): 426 (M-H)

35

C L A I M S

1. A compound of the formula:



10 in which R^1 is lower alkyl, halogen, optionally substituted heterocyclic group or optionally substituted aryl,
 R^2 is carboxy, protected carboxy or amidated carboxy,
 15 Ar is optionally substituted aryl or optionally substituted heterocyclic group,
 A is lower alkylene,
 X is oxa or a single bond,
 20 Y is thia, sulfinyl or sulfonyl,
 Z is methylene, thia, sulfinyl or sulfonyl,
 m and n are each an integer of 0 to 6, and
 $1 \leq m+n \leq 6$,
 25 and its salt.

2. The compound of claim 1, in which the heterocyclic group of R^1 and Ar are selected from the group consisting of the following (1) to (14),

- 30 (1) unsaturated 3- to 8-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms,
 (2) saturated 3- to 8-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms,
 35 (3) unsaturated 3- to 8-membered,

heteromonocyclic group containing 1 or 2
sulfur atoms,

(4) unsaturated condensed 7- to 13-membered,
heterocyclic group containing 1 to 5 nitrogen
atoms,

(5) unsaturated 3- to 8-membered,
heteromonocyclic group containing 1 or 2
oxygen atoms,

(6) saturated 3- to 8-membered, heteromonocyclic
group containing 1 or 2 oxygen atoms,

(7) unsaturated 3- to 8-membered,
heteromonocyclic group containing 1 or 2
oxygen atoms and 1 to 3 nitrogen atoms,

(8) unsaturated condensed 7- to 13-membered,
heterocyclic group containing 1 or 2 oxygen
atoms,

(9) unsaturated condensed 7- to 13-membered,
heterocyclic group containing 1 or 2 sulfur
atoms,

(10) saturated 3- to 8-membered, heteromonocyclic
group containing 1 or 2 oxygen atoms and 1 to
3 nitrogen atoms,

(11) unsaturated condensed 7- to 13-membered,
heterocyclic group containing 1 or 2 oxygen
atoms and 1 to 3 nitrogen atoms,

(12) unsaturated 3- to 8-membered,
heteromonocyclic group containing 1 or 2
sulfur atoms and 1 to 3 nitrogen atoms,

(13) saturated 3- to 8-membered, heteromonocyclic
group containing 1 or 2 sulfur atoms and 1 to
3 nitrogen atoms, and

(14) unsaturated condensed 7- to 13-membered,
heterocyclic group containing 1 or 2 sulfur
atoms and 1 to 3 nitrogen atoms, and

the aryl group of R¹ and Ar is C₆-C₁₀ aryl, and further,
each of the above-mentioned heterocyclic group and aryl group are optionally substituted by the group consisting of the following (A1) to (A35);

- (A1) halogen,
- (A2) lower alkyl,
- (A3) lower alkoxy,
- (A4) halo(lower)alkyl,
- (A5) halo(lower)alkoxy,
- (A6) lower alkenyl,
- (A7) acyl,
- (A8) lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,
- (A9) C₆-C₁₀ aryl,
- (A10) halo(C₆-C₁₀)aryl,
- (A11) hydroxy,
- (A12) hydroxy(lower)alkyl, protected hydroxy(lower)alkyl,
- (A13) amino,
- (A14) carboxy,
- (A15) protected carboxy,
- (A16) nitro(lower)alkenyl,
- (A17) lower alkylenedioxy,
- (A18) acylamino,
- (A19) nitro,
- (A20) (C₆-C₁₀)aryl(lower)alkoxy,
- (A21) carbamoyl(lower)alkenyl optionally N-substituted by the group consisting of lower alkyl, C₆-C₁₀ aryl, lower alkoxy(C₆-C₁₀)-aryl, and halo(C₆-C₁₀)aryl,
- (A22) lower alkylaminocarbonyloxy,
- (A23) lower alkanoyloxy,
- (A24) lower alkoxy(lower)alkanoyloxy,

- (A25) lower alkoxy carbonyloxy,
(A26) lower alkenoyloxy optionally substituted by
heterocyclic group of the above (1) to (14),
(A27) lower cycloalkanecarbonyloxy,
5 (A28) lower alkoxy substituted by the group
consisting of carboxy, protected carboxy,
lower alkanoyl, lower cycloalkanecarbamoyl,
and lower alkylcarbamoyl,
(A29) lower alkylcarbamoxyloxy(lower)alkyl,
10 (A30) lower alkoxy carbonylamino(lower)alkyl,
(A31) amino(lower)alkyl,
(A32) lower alkylcarbamoxyloxy(lower)alkyl,
(A33) heterocyclic-carbonylamino, the heterocyclic
group being selected from the above (1) to
15 (14) and optionally being substituted N-
protective group,
(A34) the above heterocyclic groups (1) to (14)
being optionally substituted by lower alkyl,
and
20 (A35) oxo.

3. The compound of claim 2, in which

R^1 is lower alkyl; halogen; optionally substituted
heterocyclic group consisting of the following
25 (1) to (10); or aryl consisting of phenyl and
naphthyl;

R^2 is carboxy, lower alkoxy carbonyl,
hydroxyaminocarbonyl,
tetrahydropyranyloxyaminocarbonyl, or
30 phenyl(lower)alkylaminocarbonyl,

Ar is phenyl or heterocyclic group of the following (3),
and

m and n are each an integer of 0 or 1, and $m+n=1$ or 2,
wherein the above-mentioned heterocyclic group is;

35 (1) unsaturated 5- or 6-membered heteromonocyclic

- group containing 1 to 4 nitrogen atoms,
- (2) saturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms,
- (3) unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms,
- (4) unsaturated bicyclic 9- or 10-membered, heterocyclic group containing 1 to 5 nitrogen atoms,
- (5) unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms,
- (6) saturated 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms,
- (7) unsaturated 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms,
- (8) unsaturated bicyclic 9- or 10-membered, heterocyclic group containing 1 or 2 oxygen atoms,
- (9) unsaturated bicyclic 9- or 10-membered, heterocyclic group containing 1 or 2 sulfur atoms, or
- (10) saturated 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms,

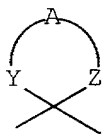
wherein the heterocyclic group being optionally substituted by the group consisting of the following (B1) to (B8);

- (B1) lower alkanoyl,
- (B2) lower alkyl,
- (B3) lower alkoxy,
- (B4) lower alkoxycarbonylamino,
- (B5) carbamoyl or lower alkylcarbamoyl,
- (B6) lower alkoxycarbonyl,
- (B7) halo, and
- (B8) oxo;

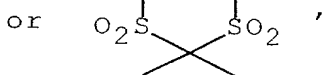
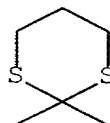
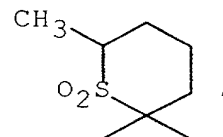
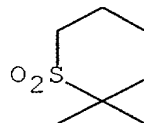
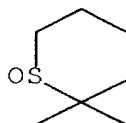
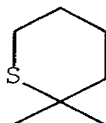
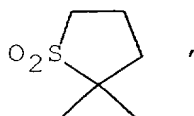
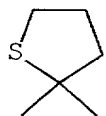
and the above-mentioned aryl is optionally

substituted by the group consisting of the (A1) to (A35) as defined in claim 2.

4. The compound of claim 3, in which
5 a group of the formula:



10 is one of the following formulae:



25 R^1 is lower alkyl; halogen; optionally substituted heterocyclic group consisting of the following (1) to (10); or aryl consisting of phenyl and naphthyl,

R^2 is carboxy, lower alkoxy carbonyl, hydroxyaminocarbonyl, or tetrahydropyranyloxyaminocarbonyl,

30 Ar is phenyl or heterocyclic group of the following (3), and

m and n are each an integer of 0 or 1, and $m+n=1$ or 2, wherein the above-mentioned heterocyclic group is

35 (1) pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl,

dihydrotriazinyl,
(2) azetidiny, pyrrolidinyl, imidazolidinyl,
piperidinyl, piperidino, pyrazolidinyl,
piperazinyl,

5

(3) thienyl,
(4) indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl, dihydrotriazolopyridazinyl,

10

(5) furyl,
(6) oxolanyl,
(7) oxazolyl, isoxazolyl, oxadiazolyl,
(8) benzofuranyl, benzodihydrofuranyl, benzodioxolenyl,
(9) benzothienyl, dihydrobenzothienyl,
(10) morpholinyl, morpholino,

15

20

wherein the heterocyclic group being optionally substituted by the group consisting of the (B1) to (B8) as defined in claim 3, and the above-mentioned aryl is optionally substituted by the group consisting of following (A1) to (A34),

25

(A1) halogen,
(A2) lower alkyl,
(A3) lower alkoxy,
(A4) halo(lower)alkyl,
(A5) halo(lower)alkoxy,

30

(A6) lower alkenyl,
(A7) acyl,
(A8) lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl,

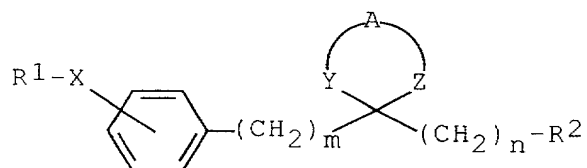
35

(A9) C₆-C₁₀ aryl
(A10) halo(C₆-C₁₀)aryl,

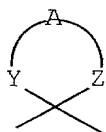
- (A11) hydroxy,
(A12) hydroxy(lower)alkyl or protected
hydroxy(lower)alkyl,
(A13) amino,
5 (A14) carboxy,
(A15) protected carboxy,
(A16) nitro(lower)alkenyl,
(A17) lower alkylenedioxy,
(A18) acylamino,
10 (A19) nitro,
(A20) (C₆-C₁₀)aryl(lower)alkoxy,
(A21) carbamoyl(lower)alkenyl optionally N-
substituted by the group consisting of lower
alkyl, (C₆-C₁₀)aryl, lower alkoxy(C₆-C₁₀)-
15 aryl, and halo(C₆-C₁₀)aryl,
(A22) lower alkylaminocarbonyloxy,
(A23) lower alkanoyloxy,
(A24) lower alkoxy(lower)alkanoyloxy,
(A25) lower alkoxycarbonyloxy,
20 (A26) lower alkenoyloxy optionally substituted by
the above heterocyclic group (1),
(A27) lower cycloalkanecarbonyloxy,
(A28) lower alkoxy substituted by the group
consisting of carboxy, protected carboxy,
25 lower alkanoyl, lower cycloalkanecarbamoyl,
and lower alkylcarbamoyl,
(A29) lower alkylcarbamoyloxy(lower)alkyl,
(A30) lower alkoxycarbonylamino(lower)alkyl,
(A31) amino(lower)alkyl,
30 (A32) lower alkylcarbamoyl(lower)alkyl,
(A33) heterocyclic-carbonylamino, the heterocyclic
group being selected from the above (2), (4)
and (5) and optionally substituted by N-
protective group, and
35 (A34) the heterocyclic group of the above (7) being

optionally substituted by lower alkyl.

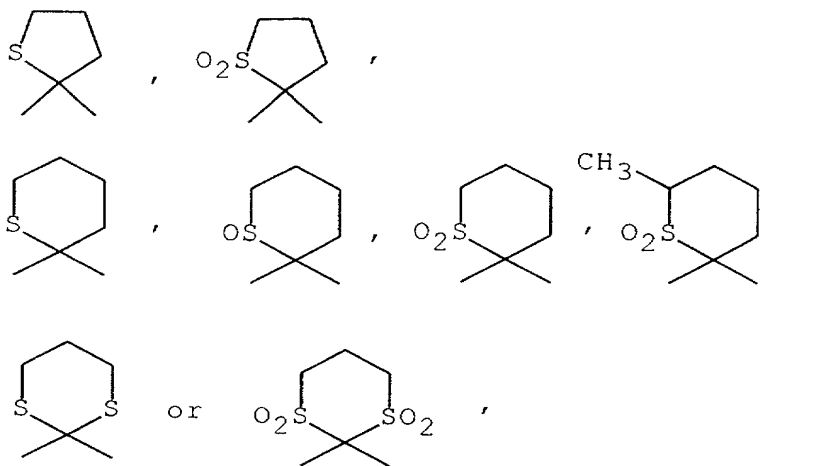
5. The compound of claim 4, having the following formula:



10 wherein a group of the formula:



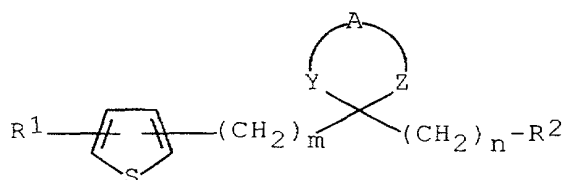
15 is one of the following formulae:



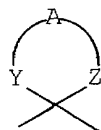
R^1 is lower alkyl, phenyl, halophenyl, or
(halo)(phenyl)phenyl,

R^2 is carboxy or hydroxyaminocarbonyl, and
m and n are each an integer of 0 or 1, and $m+n=1$.

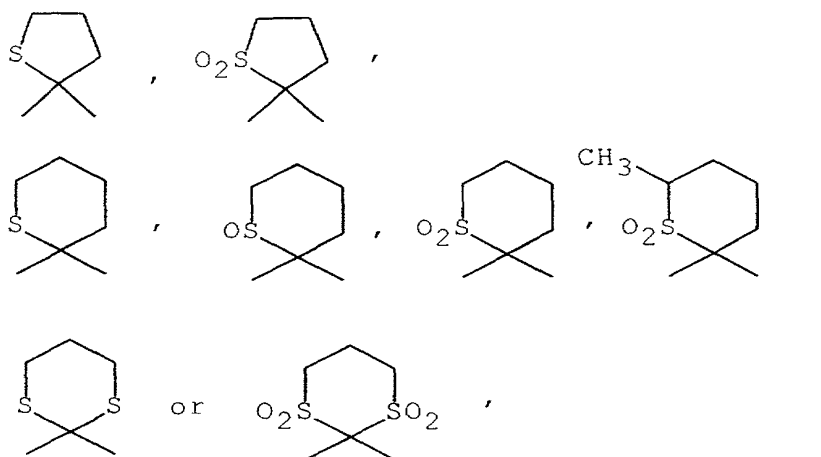
6. The compound of claim 4, having the following formula:



wherein a group of the formula:



is one of the following formulae:



R^2 is carboxy or hydroxyaminocarbonyl,

m and n are each an integer of 0 or 1, and $m+n=1$,

R^1 is halogen; heterocyclic group consisting of pyridyl, thienyl, furyl, benzofuranyl or benzothienyl, wherein the heterocyclic group is optionally substituted by the group consisting of lower alkanoyl, lower alkyl, lower alkoxy, lower alkoxy-carbonylamino and lower alkylcarbamo-yl; naphthyl or phenyl optionally substituted by the group consisting of the following (C1) to (C31);

(C1) halogen,

(C2) lower alkyl,

- (C3) lower alkoxy,
(C4) halo(lower)alkyl,
(C5) halo(lower)alkoxy,
(C6) lower alkenyl,
5 (C7) lower alkylcarbamoyl, carbamoyl,
phenyl(lower)alkylcarbamoyl, lower alkanoyl,
(C8) lower alkylthio, lower alkylsulfinyl, lower
alkylsulfonyl,
(C9) phenyl, naphthyl,
10 (C10) halophenyl,
(C11) hydroxy,
(C12) mono- or dihydroxy(lower)alkyl,
phenoxycarbonyloxy(lower)alkyl
(C13) amino,
15 (C14) carboxy,
(C15) lower alkylenedioxy,
(C16) lower alkanoylamino,
phenyl(lower)alkanoylamino,
halophenyl(lower)alkanoylamino, lower
20 alkoxy(lower)alkanoylamino,
lower alkoxy(lower)alkanoylamino,
phenoxy(lower)alkanoylamino, lower
alkoxyphenoxy(lower)alkanoylamino, lower
alkylphenoxy(lower)alkanoylamino,
25 halophenoxy(lower)alkanoylamino,
carboxy(lower)alkanoylamino, lower
alkoxycarbonyl(lower)alkanoylamino,
lower alkylcarbamoyl(lower)alkanoylamino,
halo(lower)alkanoylamino,
30 lower alkenyl(lower)alkanoylamino,
lower alkoxy(lower)alkanoylamino,
phenyl(lower)alkoxy(lower)alkanoylamino,
piperidinyloxy(lower)alkanoylamino,
N-lower alkoxycarbonylpiperidinyloxy-
35 (lower)alkanoylamino,

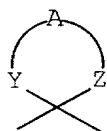
pyridyloxy(lower)alkanoylamino,
hydroxy(lower)alkanoylamino,
lower alkanoyloxy(lower)alkanoylamino,
lower alkylcarbamoyloxy(lower)alkanoylamino,
5 N,N-di(lower alkyl)carbamoyloxy,
piperidino-carbonyloxy(lower)alkanoylamino,
phenyl(lower)alkylcarbamoyloxy(lower)-
alkanoylamino, lower
alkoxycarbonylamino(lower)alkanoylamino,
10 amino(lower)alkanoylamino, lower
alkoxycarbonylamino(lower)alkanoylamino,
fluorenylmethoxycarbonylamino(lower)-
alkanoylamino,
lower alkylamino(lower)alkanoylamino, [N,N-
15 di(lower alkyl)amino](lower)alkanoylamino,
[N-lower alkyl-N-(lower alkoxycarbonyl)-
amino](lower)alkanoylamino, [N-lower alkyl-N-
(fluorenylmethoxycarbonyl)amino]-
(lower)alkanoylamino,
20 [N-lower alkyl-N-(mono- or di(lower)-
alkylcarbamoyl)amino](lower)alkanoylamino,
[N-(mono- or di(lower alkyl)carbamoyl)-
amino](lower)alkanoylamino,
benzoylamino(lower)alkanoylamino, lower
25 alkanoylamino(lower)alkanoylamino, lower
alkanesulfonylamino(lower)alkanoylamino,
lower alkoxy(lower)alkanoylamino-
(lower)alkanoylamino,
cyclo(lower)alkyloxycarbonylamino-
30 (lower)alkanoylamino,
pyridylcarbonylamino(lower)alkanoylamino,
morpholinocarbonylamino(lower)alkanoylamino,
phenyl(lower)alkoxyoxycarbonylamino-
(lower)alkanoylamino,
35 lower alkoxyphenylsulfonylamino-

(lower)alkanoylamino,
hydroxy(lower)alkylamino(lower)alkanoylamino,
morpholino(lower)alkanoylamino,
oxooxazolidinyl(lower)alkanoylamino,
5 oxopyrrolidinyl(lower)alkanoylamino,
trimethylhydantoinyl(lower)alkanoylamino,
lower alkenylamino(lower)alkanoylamino,
lower alkoxy(lower)alkylamino(lower)-
alkanoylamino,
10 phenyl(lower)alkylamino(lower)alkanoylamino,
pyridyl(lower)alkylamino(lower)alkanoylamino,
lower alkoxycarbonylamino,
phenyl(lower)alkoxycarbonylamino,
lower alkoxy(lower)alkoxycarbonylamino,
15 halo(lower)alkoxycarbonylamino,
amino(lower)alkoxycarbonylamino,
phthalimido(lower)alkoxycarbonylamino,
carbamoylamino,
(mono- or di(lower alkyl)carbamoylamino,
20 naphthylcarbamoylamino,
halophenylcarbamoylamino,
lower alkoxyphenylcarbamoylamino,
lower alkenylcarbamoylamino,
cyclo(lower)alkyl(lower)alkylcarbamoylamino,
25 phenyl(lower)alkylcarbamoylamino,
halo(lower)alkylcarbamoylamino,
lower alkoxy(lower)alkylcarbamoylamino,
hydroxy(lower)alkylcarbamoylamino, (lower
alkyl)(diphenyl)silyloxy(lower)alkyl-
30 carbamoylamino,
carboxy(lower)alkylcarbamoylamino, lower
alkoxycarbonyl(lower)alkylcarbamoylamino,
lower alkylcarbamoyl(lower)alkyl-
carbamoylamino, or
35 pyridylcarbamoylamino,

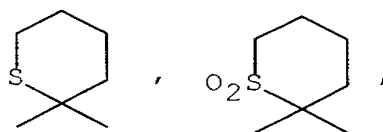
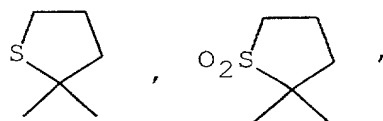
lower alkylsulfonylamino,
lower alkenoylamino,
lower cycloalkanecarbonylamino,
lower alkenyloxycarbonylamino,
5 phenoxycarbonylamino,
lower alkylthiocarbonylamino,
(C17) phenyl(lower)alkoxy,
(C18) lower alkenyl, mono- or di(lower
alkyl)carbamoyl(lower)alkenyl, (2-
10 (methylcarbamoyl)ethenyl, 2-
(ethylcarbamoyl)ethenyl, 2-
(propylcarbamoyl)ethenyl, 2-
(isopropylcarbamoyl)ethenyl, 2-
(dimethylcarbamoyl)ethenyl,)
15 phenylcarbamoyl(lower)alkenyl,
lower alkoxycarbamoyl(lower)alkenyl,
halophenylcarbamoyl(lower)alkenyl,
(C19) lower alkylaminocarbonyloxy,
(C20) lower alkanoyloxy,
20 (C21) lower alkoxy(lower)alkanoyloxy,
(C22) lower alkoxycarbonyloxy,
(C23) pyridyl(lower)alkenoyloxy
(C24) lower cycloalkanecarbonyloxy,
(C25) carboxy(lower)alkoxy,
25 lower alkoxycarbonyl(lower)alkoxy,
lower alkanoyl(lower)alkoxy,
lower cycloalkanecarbamoyl(lower)alkoxy,
lower alkylcarbamoyl(lower)alkoxy,
(C26) lower alkylcarbamoyloxy(lower)alkyl,
30 (C27) lower alkoxycarbonylamino(lower)alkyl,
(C28) amino(lower)alkyl,
(C29) lower alkylcarbamoyl(lower)alkyl,
(C30) furylcarbonylamino,
teretahydroisoquinolylcarbonylamino,
35 N-lower alkoxycarbonyl-

teretahydroisoquinolylcarbonylamino,
 pyrrolidinylcarbonylamino,
 (C31) oxazolyl, lower alkyloxadiazolyl.

- 5 7. The compound of claim 6, in which
 a group of the formula:

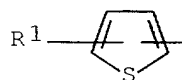


10 is one of the following formulae:



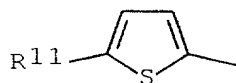
15 R^2 is hydroxyaminocarbonyl,
 20 m is 0 and n is 1,

a group of the formula:



is the group of the following formulae (a) to (e);

25 (a)



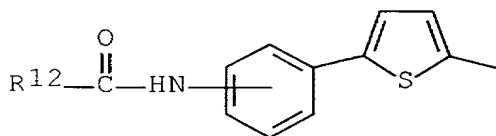
30 wherein

R^1 is halo, naphtyl, phenyl, mono- or dihalophenyl,
 mono- or di(lower)alkylphenyl, lower alkoxyphenyl,
 trihalo(lower)alkylphenyl,
 trihalo(lower)alkoxyphenyl, lower alkenylphenyl,
 35 lower alkylcarbamoylphenyl, carbamoylphenyl,

phenyl(lower)alkylcarbamoylphenyl, lower
alkanoylphenyl, lower alkylthiophenyl, lower
alkylsulfinylphenyl, lower alkylsulfonylphenyl,
phenylphenyl, (halo)(phenyl)phenyl, halophenylphenyl,
5 hydroxyphenyl, mono- or dihydroxy(lower)alkylphenyl,
phenoxycarbonyloxy(lower)alkylphenyl, aminophenyl,
carboxyphenyl, lower alkylendioxyphenyl, lower
alkanesulfonylaminophenyl, lower alkenoylaminophenyl,
lower cycloalkanecarbonylaminophenyl,
10 phenyl(lower)alkoxyphenyl, mono- or di(lower
alkyl)carbamoyl(lower)alkenylphenyl,
phenylcarbamoyl(lower)alkenylphenyl,
lower alkoxy carbamoyl(lower)alkenylphenyl,
halophenylcarbamoyl(lower)alkenylphenyl, lower
15 alkylcarbamoxyloxyphenyl, lower alkanoyloxyphenyl,
lower alkoxy(lower)alkanoyloxyphenyl, lower
alkoxycarbonyloxyphenyl,
pyridyl(lower)alkenoyloxyphenyl,
cyclo(lower)alkylcarbonyloxyphenyl,
20 carboxy(lower)alkoxyphenyl, lower
alkoxycarbonyl(lower)alkoxyphenyl, lower
alkanoyl(lower)alkoxyphenyl, lower
cycloalkanecarbamoyl(lower)alkoxyphenyl, lower
alkylcarbamoyl(lower)alkoxyphenyl, lower
25 alkylcarbamoxyloxy(lower)alkylphenyl, lower
alkoxycarbonylamino(lower)alkylphenyl,
amino(lower)alkylphenyl, lower
alkylcarbamoyl(lower)alkylphenyl,
furylcarbonylaminophenyl, 1,2,3,4-
30 teretahydroisoquinolylcarbonylaminophenyl,
N-t-butoxycarbonyl, 1,2,3,4-
teretahydroisoquinolylcarbonylaminophenyl,
pyrrolidinylcarbonylaminophenyl, oxazolylphenyl,
lower alkyloxadiazolylphenyl.

(b)

5



wherein

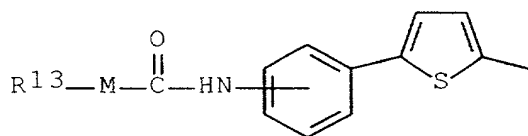
10

R^{12} is lower alkyl optionally substituted by the group
 consisting of phenyl, halophenyl, lower
 alkoxyphenyl, lower alkoxy, phenoxy, lower
 alkoxyphenoxy, halophenoxy, lower alkylphenoxy,
 carboxy, lower alkoxycarbonyl, lower alkylcarbamoyl,
 halo, lower alkenyloxy, lower alkoxy(lower)alkoxy,
 15 phenyl(lower)alkoxy, piperidinyloxy, N-lower
 alkoxycarbonyl-piperidinyloxy, pyridyloxy, hydroxy,
 lower alkanoyloxy, mono- or
 di(lower)alkylcarbamoxyloxy, piperidinylcarbonyloxy,
 phenyl(lower)alkylcarbamoxyloxy, lower
 20 alkoxycarbonylamino, amino, lower
 alkoxycarbonylamino, fluorenylmethoxycarbonylamino,
 mono- or di(lower)alkylamino, N-lower alkyl-N-
 (lower alkoxycarbonyl)amino, N-lower alkyl-N-
 (fluorenylmethoxycarbonyl)amino, N-lower alkyl-N-
 25 (mono- or di(lower)alkylcarbamoxy)amino, N-(mono-
 or di(lower alkyl)carbamoxy)amino, benzoylamino,
 lower alkanoylamino, lower alkanesulfonylamino,
 lower alkoxy(lower)alkanoylamino,
 cyclo(lower)alkyloxycarbonylamino,
 30 pyridylcarbonylamino, morpholinocarbonylamino,
 phenyl(lower)alkoxyoxycarbonylamino, lower
 alkoxyphenylsulfonylamino, hydroxy(lower)alkylamino,
 morpholino, oxooxazolidinyl, oxopyrrolidinyl,
 trimethylhydantoinyl, pyridyl, lower alkenylamino,
 35 lower alkoxy(lower)alkylamino,

phenyl(lower)alkylamino, pyridyl(lower)alkylamino,
and cyclo(lower)alkyl,

(c)

5



wherein

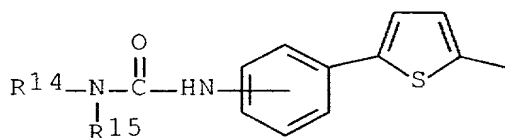
10

M is oxygen or sulfur,

R^{13} is lower alkyl, phenyl(lower)alkyl,
lower alkoxy(lower)alkyl, halo(lower)alkyl,
amino(lower)alkyl, or
phthalimido(lower)alkoxycarbonylamino,
15 lower alkenyl, phenyl,

(d)

20



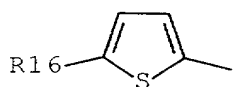
wherein

R^{15} is hydrogen or lower alkyl,

R^{14} is hydrogen, lower alkyl, naphthyl, halophenyl,
25 lower alkoxyphenyl, lower alkenyl, lower
cycloalkyl(lower)alkyl, phenyl(lower)alkyl,
halo(lower)alkyl, lower alkoxy(lower)alkyl,
hydroxy(lower)alkyl, (lower
alkyl)(diphenyl)silyloxy(lower)alkyl,
30 carboxy(lower)alkyl, lower
alkoxycarbonyl(lower)alkyl, lower
alkylcarbamoyl(lower)alkyl, or pyridyl,

(e)

35

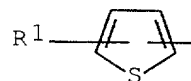


wherein

- 5 R^{16} is benzothienyl, benzofuranyl, thienyl, furyl, lower alkylpyridyl, pyridyl, lower alkoxy pyridyl, lower alkoxy carbonylaminopyridyl, lower alkanoylthienyl, lower alkylcarbamoylbenzofuranyl.

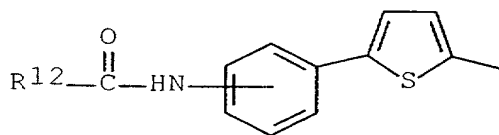
- 10 8. The compound of claim 7, wherein

a group of the formula:



is the same group as (a), (c), (d) and (e) of claim 7,
15 and the following formula (b):

(b)



wherein

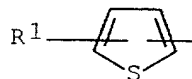
- 20 R^{12} is lower alkyl, phenyl(lower)alkyl, halophenyl(lower)alkyl, lower alkoxyphenyl(lower)alkyl,
25 lower alkoxy(lower)alkyl, phenoxy(lower)alkyl, lower alkoxyphenoxy(lower)alkyl, halophenoxy(lower)alkyl, lower alkylphenoxy(lower)alkyl, carboxy(lower)alkyl, lower alkoxy carbonyl(lower)alkyl,
30 lower alkylcarbamoyl(lower)alkyl, halo(lower)alkyl, lower alkenyloxy(lower)alkyl, lower alkoxy(lower)alkoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, piperidinyloxy(lower)alkyl,
35 N-t-butoxycarbonylpiperidinyloxy(lower)alkyl,

pyridyloxy(lower)alkyl, hydroxy(lower)alkyl,
lower alkanoyloxy(lower)alkyl,
mono- or di(lower)alkylcarbamoyloxy(lower)alkyl,
piperidinylcarbonyloxy(lower)alkyl,
5 phenyl(lower)alkylcarbamoyloxy(lower)alkyl,
lower alkoxycarbonylamino(lower)alkyl,
amino(lower)alkyl,
lower alkoxycarbonylamino(lower)alkyl,
fluorenylmethoxycarbonylamino(lower)alkyl,
10 mono- or di(lower)alkylamino(lower)alkyl,
N-lower alkyl-N-(lower
alkoxycarbonyl)amino(lower)alkyl,
N-lower alkyl-N-(fluorenylmethoxycarbonyl)amino-
(lower)alkyl, N-lower alkyl-N-(mono- or di(lower)-
15 alkylcarbamoyl)amino(lower)alkyl, N-(mono- or
di(lower alkyl)carbamoyl)amino(lower)alkyl,
benzoylamino(lower)alkyl,
lower alkanoylamino(lower)alkyl,
lower alkanesulfonylamino(lower)alkyl,
20 lower alkoxy(lower)alkanoylamino(lower)alkyl,
cyclo(lower)alkyloxycarbonylamino(lower)alkyl,
pyridylcarbonylamino(lower)alkyl,
morpholinocarbonylamino(lower)alkyl,
phenyl(lower)alkoxyoxycarbonylamino(lower)alkyl,
25 lower alkoxyphenylsulfonylamino(lower)alkyl,
hydroxy(lower)alkylamino(lower)alkyl,
morpholino(lower)alkyl, oxooxazolidinyl(lower)alkyl,
oxopyrrolidinyl(lower)alkyl,
trimethylhydantoinyl(lower)alkyl,
30 pyridyl(lower)alkyl, lower alkenylamino(lower)alkyl,
lower alkoxy(lower)alkylamino(lower)alkyl,
phenyl(lower)alkylamino(lower)alkyl,
pyridyl(lower)alkylamino(lower)alkyl,
cyclo(lower)alkyl, (amino)(phenyl)(lower)alkylamino,
35 (lower alkoxycarbonylamino)(phenyl)(lower)alkyl,

(amino)(lower alkoxy)(lower)alkyl, (lower
 alkoxy-carbonylamino)(lower alkoxy)(lower)alkyl,
 (amino)(carboxy)(lower)alkyl, (lower
 alkoxy-carbonylamino)(carboxy)(lower)alkyl,
 (amino)(lower alkoxy-carbonyl)(lower)alkyl, (lower
 alkoxy-carbonylamino)(lower alkoxy-carbonyl)-
 (lower)alkyl, (amino)(phenyl(lower)alkoxy)-
 (lower)alkyl, (lower alkoxy-carbonylamino)-
 (phenyl(lower)alkoxy)(lower)alkyl,
 (amino)(pyridyl)(lower)alkyl,
 (lower alkoxy-carbonylamino)(pyridyl)(lower)alkyl,
 (amino)(hydroxy)(lower)alkyl, (lower
 alkoxy-carbonylamino)(hydroxy)(lower)alkyl,
 (amino)(amino)(lower)alkyl,
 (lower alkoxy-carbonylamino)(amino)(lower)alkyl,
 (amino)(lower alkoxy-carbonylamino)(lower)alkyl,
 (lower alkoxy-carbonylamino)(lower
 alkoxy-carbonylamino)(lower)alkyl,
 (amino)(lower cycloalkane)(lower)alkyl,
 (lower alkoxy-carbonylamino)(lower
 cycloalkane)(lower)alkyl.

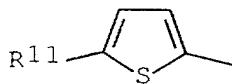
9. The compound of claim 7, in which

a group of the formula:



is the group of the following formula (a) to (e):

(a)

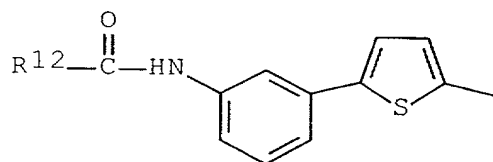


wherein

R¹¹ is bromo, 2-naphthyl, phenyl,
3(or 4)-chlorophenyl, 2(or 3 or 4)-fluorophenyl,
3,4-dichlorophenyl, 3,5-difluorophenyl,
3(or 4)-methylphenyl, 4-ethylphenyl,
5 4-isopropylphenyl, 4-(t-butyl)phenyl,
3,4-dimethylphenyl, 4-methoxyphenyl,
4-ethoxyphenyl, 4-trifluoromethylphenyl,
4-trifluoromethoxyphenyl, 4-ethenylphenyl,
4-methylcarbamoylphenyl, 4-ethylcarbamoylphenyl, 4-
10 carbamoylphenyl, 4-benzylcarbamoylphenyl,
4-acetylphenyl, 4-methylthiophenyl,
4-ethylthiophenyl, 4-methylsulfinylphenyl,
4-methylsulfonylphenyl, phenylphenyl, 4-phenyl-3-
15 fluorophenyl, 4-(4-fluorophenyl)phenyl, 3(or 4)-
hydroxyphenyl, 3(or 4)-hydroxymethylphenyl,
4-(1,2-dihydroxyethyl)phenyl,
4-(phenoxycarbonyloxymethyl)phenyl, 3(or 4)-
aminophenyl, 4-carboxyphenyl,
3,4-methylenedioxyphenyl,
20 4-(methanesulfonylamino)phenyl,
3-(2-butenoylamino)phenyl,
3-(cyclopropanecarbonylamino)phenyl,
3-(cyclobutanecarbonylamino)phenyl,
3-(cyclopentanecarbonylamino)phenyl,
25 4-benzyloxyphenyl,
4-(2-(methylcarbamoyl)ethenyl)phenyl,
4-(2-(ethylcarbamoyl)ethenyl)phenyl,
4-(2-(propylcarbamoyl)ethenyl)phenyl,
4-(2-(isopropylcarbamoyl)ethenyl)phenyl,
30 4-2-(dimethylcarbamoyl)ethenyl)phenyl,
4-(2-(phenylcarbamoyl)ethenyl)phenyl,
4-(2-(methoxyphenylcarbamoyl)ethenyl)phenyl,
4-(2-(4-fluorophenylcarbamoyl)ethenyl)phenyl,
4-(methylaminocarbonyloxy)phenyl,
35 4-(ethylaminocarbonyloxy)phenyl,

4-propanoyloxyphenyl, 4-(methoxyacetyloxy)phenyl,
 4-(ethoxycarbonyloxy)phenyl,
 4-(3-(3-pyridyl)acryloyloxy)phenyl,
 4-(cyclopropylcarbonyloxy)phenyl,
 5 4-(carboxymethoxy)phenyl,
 4-(ethoxycarbonylmethoxy)phenyl,
 4-(t-butoxycarbonylmethoxy)phenyl,
 4-(propanoylmethoxy)phenyl,
 4-(cyclopropylcarbamoylemethoxy)phenyl,
 10 3(or 4)-(methylcarbamoylemethoxy)phenyl,
 4-(ethylcarbamoylemethoxy)phenyl,
 4-(propylcarbamoylemethoxy)phenyl,
 3(or 4)-(methylcarbamoyleoxymethyl)phenyl,
 4-(methoxycarbonylaminomethyl)phenyl,
 15 4-(t-butoxycarbonylaminomethyl)phenyl,
 4-aminomethylphenyl,
 4-(methylcarbamoylemethyl)phenyl,
 3-(2(or 3)-furylcarbonylamino)phenyl, 3-(1,2,3,4-
 teretahydroisoquinolylcarbonylamino)phenyl,
 20 3-(N-(t-butoxycarbonyl)-1,2,3,4-
 teretahydroisoquinolylcarbonylamino)phenyl,
 3-(pyrrolidinylcarbonylamino)phenyl,
 4-(1,3-oxazolyl)phenyl,
 4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl,

(b)



wherein

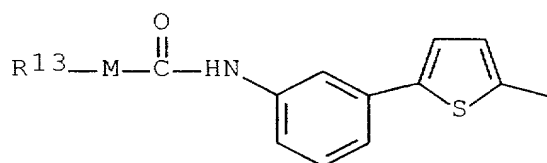
R^{12} is methyl, ethyl, propyl, isopropyl, butyl,
 isobutyl, t-butyl, neopentyl, phenylmethyl,
 35 4-chlorophenylmethyl, 4-methoxyphenylmethyl,

methoxymethyl, ethoxymethyl, propoxymethyl,
butoxymethyl, isopropylloxymethyl, 1-methoxyethyl,
2-methoxyethyl, phenoxyethyl, 2-phenoxyethyl, 3(or
4)-methoxyphenoxymethyl, 4-fluoro(or
5 chloro)phenoxyethyl, 3(or 4)-methylphenoxyethyl,
2-carboxyethyl, 2-methoxycarbonylethyl, 2-t-
butoxycarbonylethyl, 2-methylcarbamoylethyl,
2-chloroethyl, chloromethyl, allyloxymethyl,
(2-ethoxyethoxy)methyl, benzyloxymethyl,
10 4-piperidinylloxymethyl, (N-t-butoxycarbonyl-4-
piperidinyl)oxymethyl, 3(or 4)-pyridylloxymethyl,
hydroxymethyl, 2-hydroxyethyl, acetoxymethyl,
1-acetoxyethyl, methylcarbamoyloxymethyl, 1-(N-
methyl-N-ethylcarbamoyloxy)methyl, (piperidino-
15 carbonyloxy)methyl, (benzylcarbamoyloxy)methyl,
(t-butoxycarbonylamino)methyl, aminomethyl,
1-aminoethyl, 1-(t-butoxycarbonylamino)ethyl,
2-aminoethyl, methoxycarbonylaminomethyl,
2-(methoxycarbonylamino)ethyl,
20 ethoxycarbonylaminomethyl,
propoxycarbonylaminomethyl,
1-(fluorenylmethoxycarbonylamino)methyl,
2-(t-butoxycarbonylamino)ethyl,
2-(fluorenylmethoxycarbonylamino)ethyl,
25 1-aminoisopropyl, 1-aminopropyl,
1-(t-butoxycarbonylamino)propyl,
1-(t-butoxycarbonylamino)isopropyl,
1,5-diaminopentyl, 1,5-bis(t-butoxycarbonylamino)-
pentyl, methylaminomethyl, ethylaminomethyl,
30 3-(2-(N-methyl-N-ethylamino)methyl,
3-(dimethylaminomethyl, 3-(pentylaminomethyl,
3-(t-butylaminomethyl, 3-(3-methylaminoethyl,
3-(2-(N-methyl-N-methoxycarbonylamino)methyl,
1-(N-methyl-N-t-butoxycarbonylamino)methyl,
35 1-(N-ethyl-N-t-butoxycarbonylamino)methyl,

2-(N-methyl-N-(fluorenylmethoxycarbonyl)amino)-
ethyl, 2-(N-methyl-N-(t-butoxycarbonyl)amino)ethyl,
1-(N-methyl-N-(dimethylcarbamoyle)amino)methyl,
1-(dimethylcarbamoyleamino)methyl,
5 1-(N-(ethylcarbamoyle)amino)methyl,
2-(N-(ethylcarbamoyle)amino)ethyl,
benzoylaminomethyl, 2-benzoylaminoethyl,
acetylaminomethyl, isobutyrylaminomethyl,
pivaloylaminomethyl,
10 1-(methanesulfonylamino)methyl,
2-(methanesulfonylamino)ethyl,
methoxyacetylaminomethyl,
cyclopentyloxycarbonylaminomethyl,
pyridylcarbonylaminomethyl,
15 morpholinocarbonylaminomethyl,
benzyloxycarbonylaminomethyl,
1-(4-methoxyphenylsulfonylamino)methyl,
1-(2-hydroxyethylamino)methyl,
morpholinomethyl, 1-(2-oxo-1,3-oxazolidin-1-
20 yl)methyl, 1-(2-oxopyrrolidin-1-yl)methyl,
1-(3,4,4-trimethylhydantoin-1-yl)methyl,
allylaminomethyl, 1-(2-ethoxyethylamino)methyl,
benzylaminomethyl, 1-(3-pyridylmethylamino)methyl,
2-phenyl-1-aminoethyl, 1-amino-1-phenylmethyl,
25 1-t-butoxycarbonylamino-1-phenylmethyl,
1-amino-2-phenylethyl, 1-t-butoxycarbonylamino-2-
phenylethyl, 1-amino-2-methoxyethyl,
1-t-butoxycarbonylamino-2-methoxyethyl, 1-amino-3-
carboxypropyl, 1-t-butoxycarbonylamino-3-
30 carboxypropyl, 1-amino-3-(t-butoxycarbonyl)propyl,
1-t-butoxycarbonylamino-3-t-butoxycarbonylpropyl,
etc.), 1-amino-2-benzyloxyethyl,
1-t-butoxycarbonylamino-2-benzyloxyaminoethyl,
1-amino-2-(3-pyridyl)ethyl, 1-t-
35 butoxycarbonylamino-2-(3-pyridyl)ethyl, 1-amino-2-

(4-pyridyl)ethyl, 1-t-butoxycarbonylamino-2-(4-pyridyl)ethyl, 1-amino-2-hydroxyethyl, 1-t-butoxycarbonylamino-2-hydroxyethyl, (1,5-diaminopentyl, 1-t-butoxycarbonylamino-5-aminopentyl, 1,5-bis(t-butoxycarbonylamino)pentyl, 1-amino-5-(t-butoxycarbonylamino)pentyl, 1-amino-2-cyclohexylethyl, 1-t-butoxycarbonylamino-2-cyclohexylethyl,

10 (c)



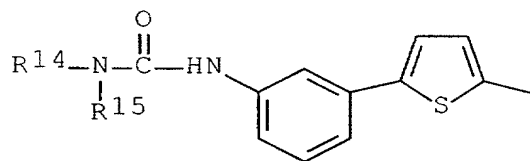
15

wherein

M=O and R¹³ is methyl, ethyl, propyl, isopropyl, benzyl, 2-methoxyethyl, 2-chloroethyl, 2-aminoethyl, 2-phthalimidoethyl, allyl, phenyl, or
M=S and R¹³ is methyl, ethyl,

20

(d)



25

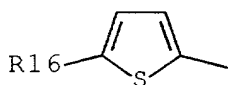
wherein

R¹⁵ is hydrogen and
R¹⁴ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, 1-naphthyl, 3(or 4)-chlorophenyl, 3-methoxyphenyl, allyl, cyclohexylmethyl, benzyl, 2-chloroethyl, methoxymethyl, 2-methoxyethyl, 2-hydroxyethyl, 2-((t-butyl)(diphenyl)silyloxy)ethyl, carboxymethyl, ethoxycarbonylmethyl,

35

methylcarbamoylmethyl, or 3-pyridyl,
 R^{14} is ethyl and R^{15} is methyl,

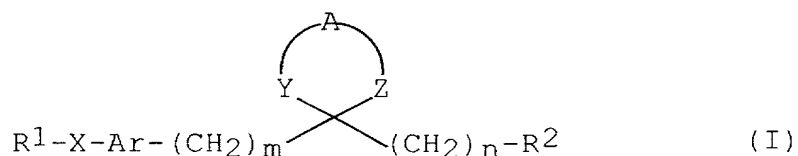
(e)



wherein

R^{16} is 2-benzothieryl, 2-benzofuranyl, 2(or 3)-thienyl,
 2-furyl, 3-pyridyl, 1-methyl-4-pyridyl, 6-methyl-3-
 pyridyl, 6-methoxy-3-pyridyl,
 5-methoxycarbonylamino-3-pyridyl, 5-acetyl-2-
 thienyl, 2-methylcarbamoyl-5-benzofuranyl.

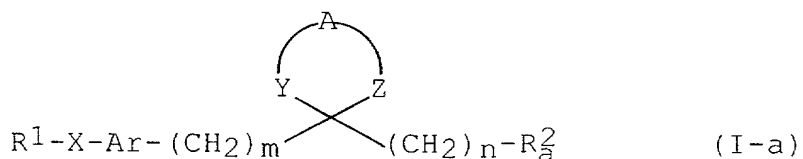
10. A process for the preparation of a compound of the
 formula:



25 in which R^1 , R^2 , Ar, A, X, Y, Z, m and n are each as
 defined in Claim 1,

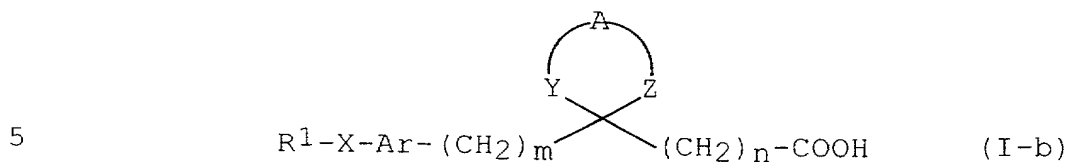
which comprises

30 (1) subjecting a compound of the formula:



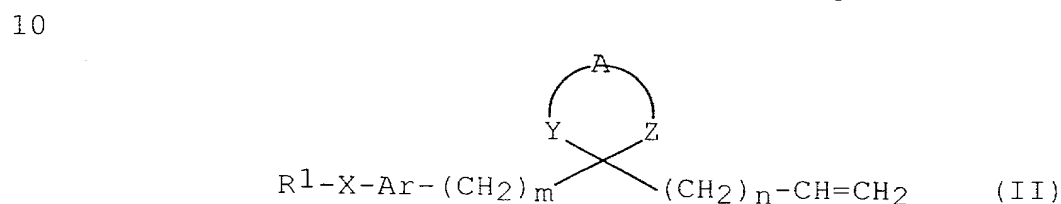
or a salt thereof to removal reaction of the carboxy-

protective group, to give a compound of the formula:



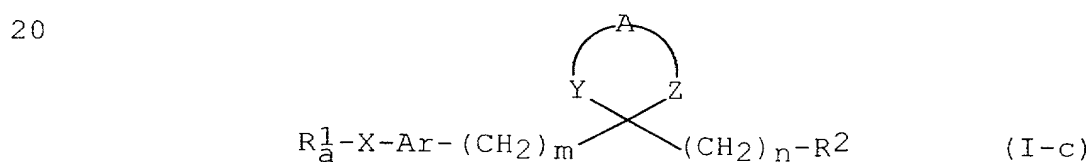
or a salt thereof; or

(2) oxidating the vinyl group of a compound of the formula:

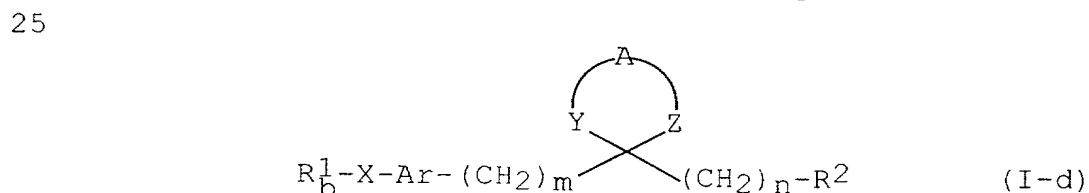


15 or a salt thereof, to give a compound of the above formula (I-b) or a salt thereof; or

(3) reducing a compound of the formula:



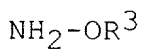
or a salt thereof, to give a compound of the formula:



30 or a salt thereof; or

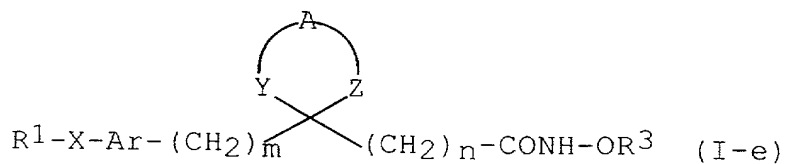
(4) reacting a compound of the above formula (I-b) or its reactive derivative at the carboxy-group, or a salt thereof, with a compound of the formula:

35



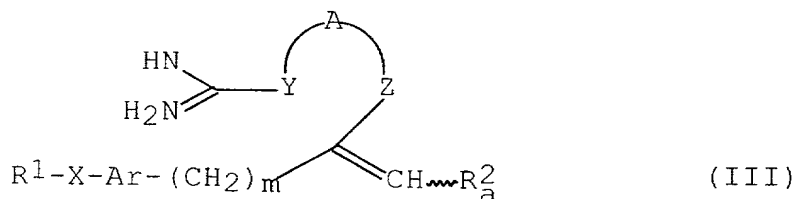
(IV)

or its reactive derivative at the amino-group,
or a salt thereof, to give a compound of the formula:

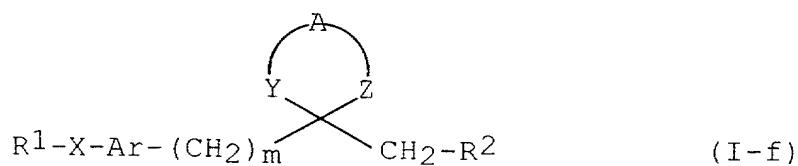


or a salt thereof; or

(5) cyclizing a compound of the formula:

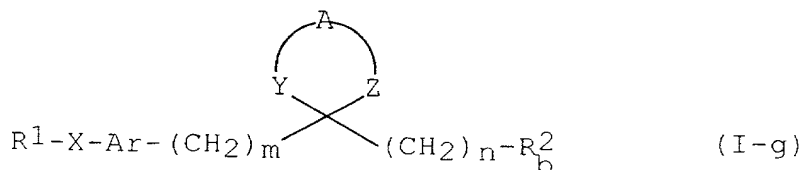


or a salt thereof, to give a compound of the formula:



or a salt thereof; or

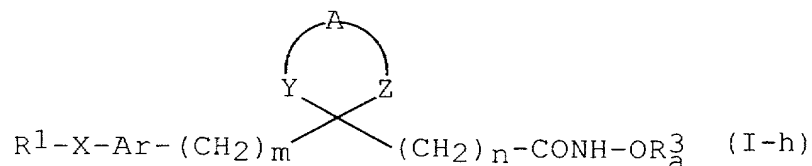
(6) reacting a compound of the above formula (I-b) or its
reactive derivative at the carboxy-group, or a salt
thereof, with an optically active amine or its reactive
derivative at the amino-group, or a salt thereof, to
give a compound of the formula:



or a salt thereof; or

(7) subjecting a compound of the formula:

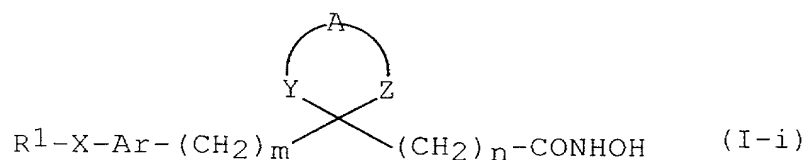
5



10

or a salt thereof to removal reaction of the hydroxy-protective group, to give a compound of the formula:

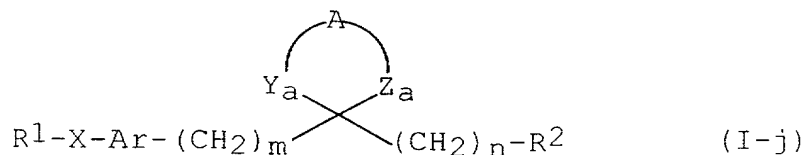
15



or a salt thereof; or

(8) oxidating a compound of the formula:

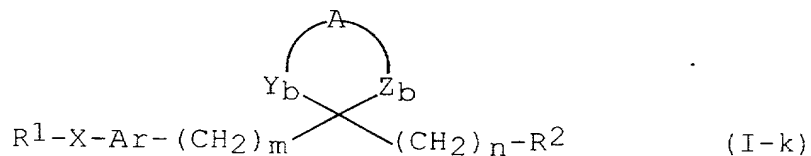
20



25

or a salt thereof, to give a compound of the formula:

30

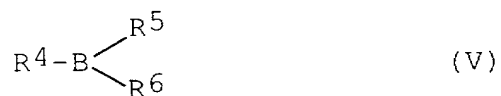


or a salt thereof; or

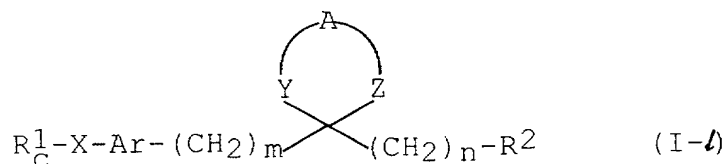
(9) reacting a compound of the above formula (I-c)

or a salt thereof, with a compound of the formula:

35



5 to give a compound of the formula:



10

or a salt thereof; or

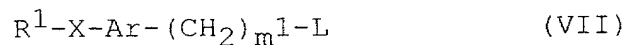
(10) reacting a compound of the formula:

15



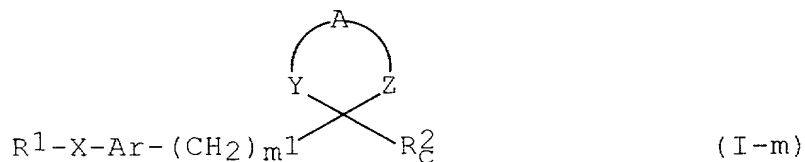
20

or a salt thereof, with a compound of the formula:



or a salt thereof, to give a compound of the formula:

25

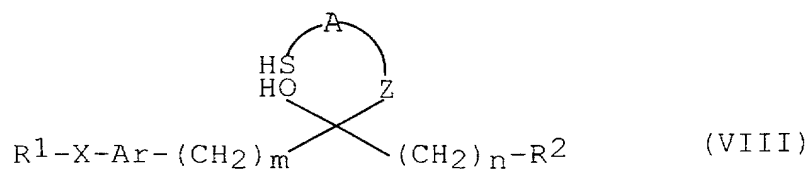


30

or a salt thereof; or

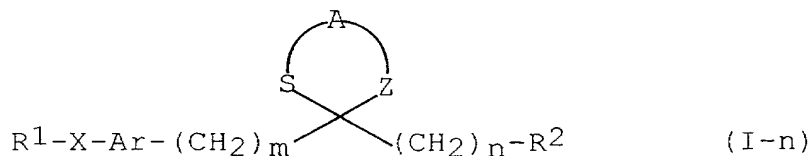
(11) cyclizing a compound of the formula:

35



5

or a salt thereof, to give a compound of the formula:

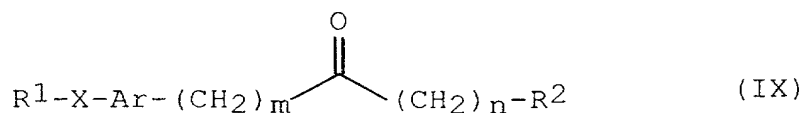


10

or a salt thereof; or

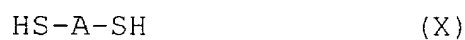
(12) reacting a compound of the formula:

15



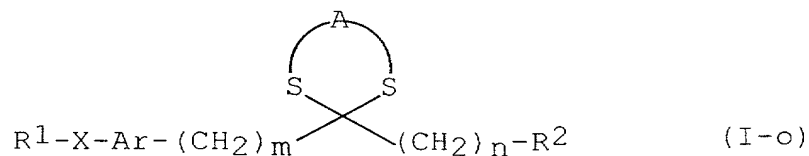
20

or a salt thereof, with a compound of the formula:



to give a compound of the formula:

25

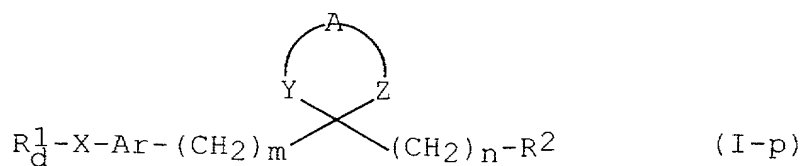


30

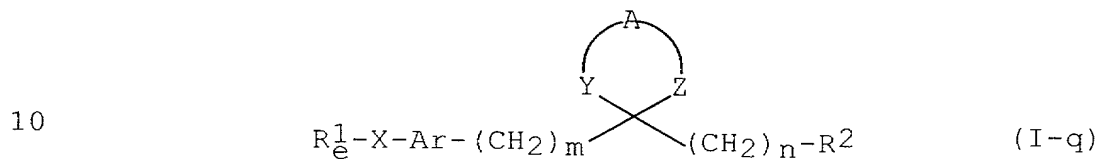
or a salt thereof; or

(13) amidating a compound of the formula:

35

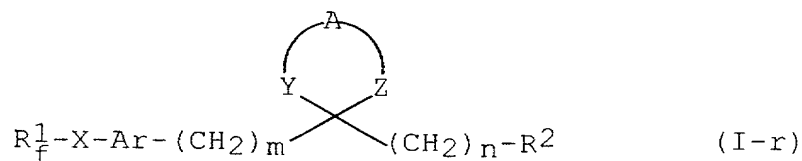


5 or its reactive derivative at the carboxy group,
or a salt thereof, to give a compound of the formula:

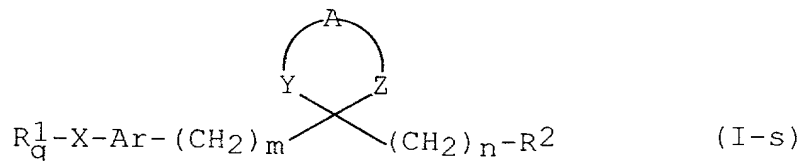


or a salt thereof; or

(14) acylating a compound of the formula:

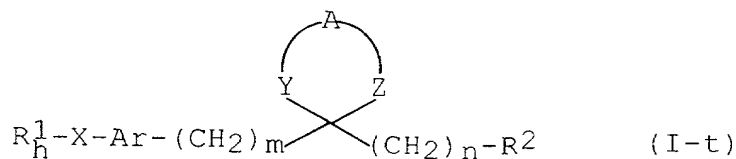


20 or its reactive derivative at the amino group,
or a salt thereof, to give a compound of the formula:

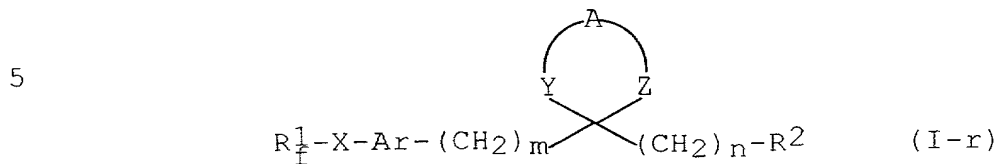


or a salt thereof; or

(15) subjecting a compound of the formula:

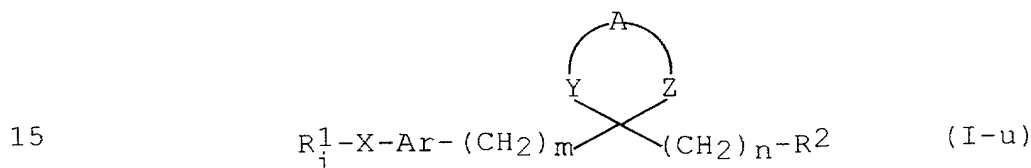


or a salt thereof to a removal reaction of the amino-protective group, to give a compound of the formula:

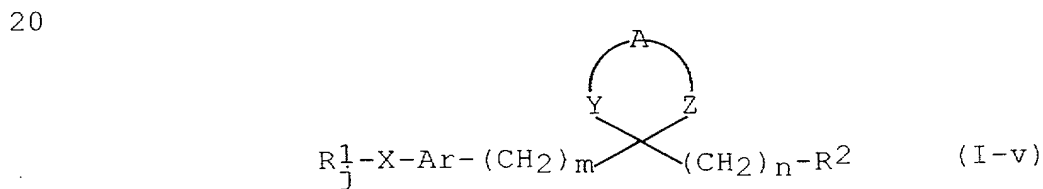


or a salt thereof; or

10 (16) subjecting a compound of the formula:

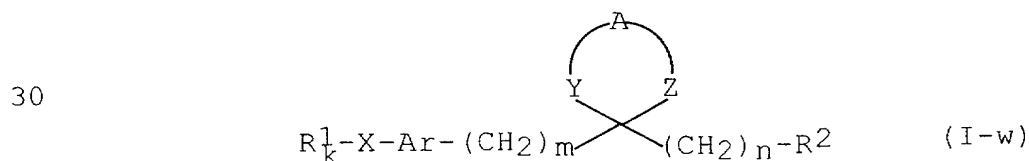


or a salt thereof to a removal reaction of the hydroxy-protective group, to give a compound of the formula:



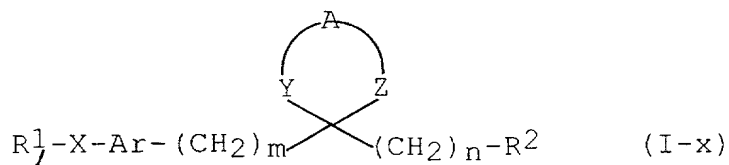
25 or a salt thereof; or

(17) oxidating a compound of the formula:



or a salt thereof, to give a compound of the formula:

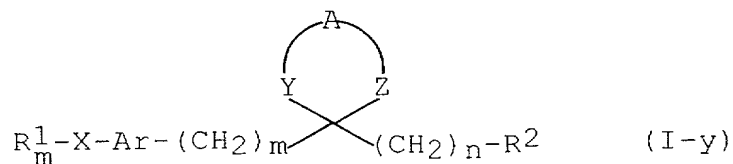
35



5

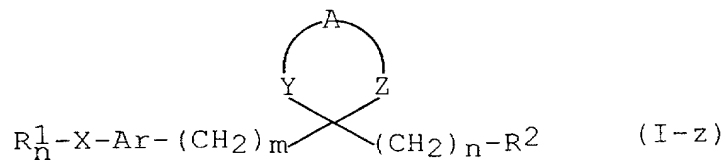
or a salt thereof; or

(18) reducing a compound of the formula:



10

or a salt thereof, to give a compound of the formula:

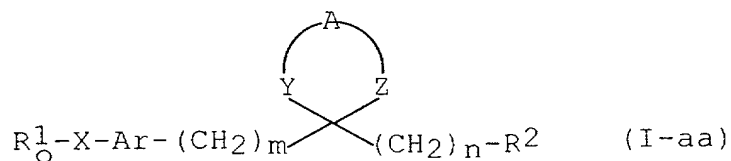


15

20

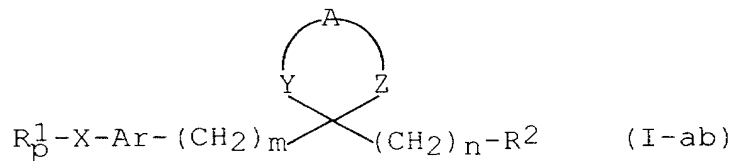
or a salt thereof; or

(19) oxidating a compound of the formula:



25

or a salt thereof, to give a compound of the formula:

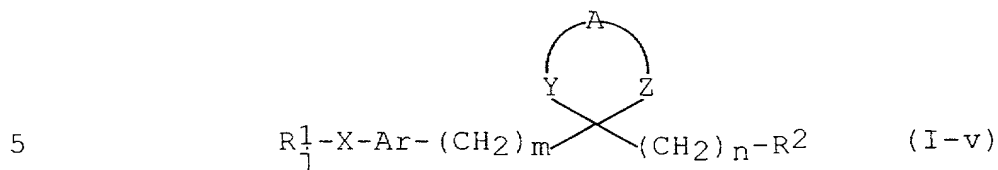


30

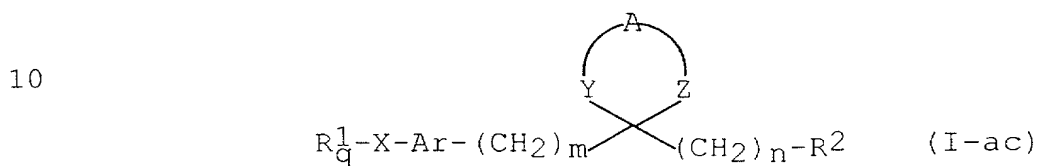
or a salt thereof; or

35

(20) acylating a compound of the formula:

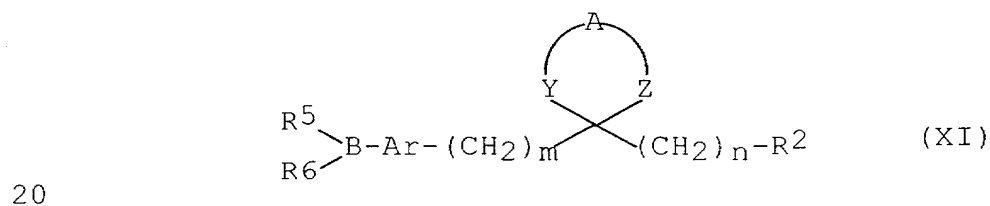


or a salt thereof, to give a compound of the formula:



or a salt thereof; or

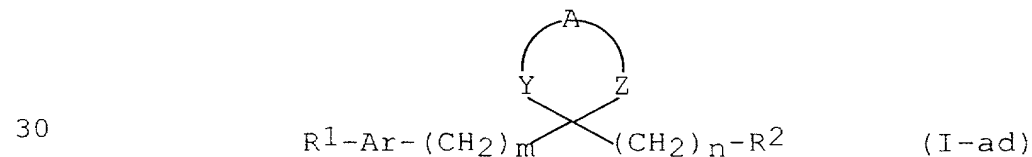
15 (21) reacting a compound of the formula:



or a salt thereof, with a compound of the formula:



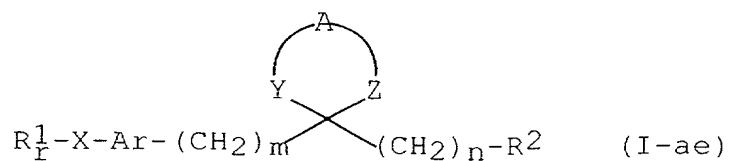
or a salt thereof, to give a compound of the formula:



or a salt thereof; or

(22) subjecting a compound of the formula:

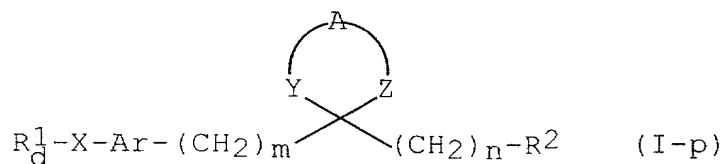
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or a salt thereof, to a removal reaction of the carboxy-protective group, to give a compound of the formula:

10

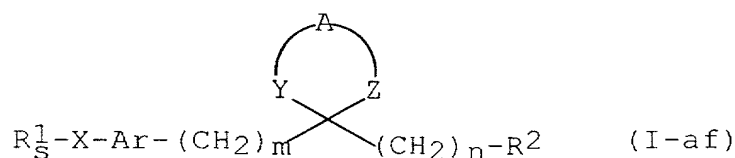


or a salt thereof; or

15

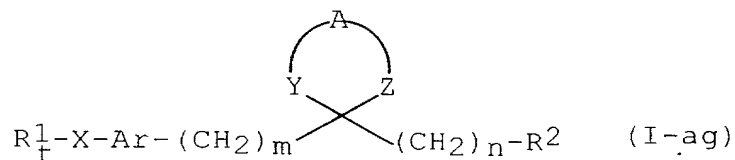
(23) reacting a compound of the formula:

20



or a salt thereof, with a substituted amine, to give a compound of the formula:

25



or a salt thereof,

30

in which R^1 , R^2 , Ar, A, X, Y, Z, m and n are each as defined above,

R_a^1 is haloaryl or halo,

R_b^1 is aryl,

35

R_c^1 is aryl at least substituted by optionally

substituted aryl,

R_d^1 is aryl at least having carboxy moiety,

R_e^1 is aryl at least having amido moiety,

R_f^1 is aryl at least having amino moiety,

5 R_g^1 is aryl at least having acylamino moiety,

R_h^1 is aryl at least having protected amino moiety,

R_i^1 is aryl at least having protected hydroxy moiety,

R_j^1 is aryl at least having hydroxy moiety,

R_k^1 is aryl at least having thia moiety,

10 R_l^1 is aryl at least having sulfinyl or

sulfonyl moiety,

R_m^1 is aryl at least having formyl moiety,

R_n^1 is aryl at least having hydroxymethyl moiety,

R_o^1 is aryl at least having vinyl moiety,

15 R_p^1 is aryl at least having 1,2-dihydroxyethyl moiety,

R_q^1 is aryl at least having acyloxy moiety,

R_r^1 is aryl at least having protected

carboxy moiety,

R_s^1 is aryl at least having halo(lower)alkanoyl

20 moiety,

R_t^1 is aryl at least having substituted

amino(lower)alkanoyl moiety,

R_a^2 is protected carboxy,

R_b^2 is optically active amide,

25 R_c^2 is protected carboxy,

R^3 is hydrogen or hydroxy-protective group,

R_a^3 is hydroxy-protective group,

R^4 is optionally substituted aryl,

R^5 and R^6 are each hydrogen or combined together to

30 form lower alkylene,

Y_a is thia, sulfinyl or sulfonyl,

Z_a is methylene, thia, sulfinyl or sulfonyl,

provided that at least one of

Y_a and Z_a is thia or sulfinyl,

35 Y_b is thia, sulfinyl or sulfonyl,

Z_b is methylene, thia, sulfinyl or sulfonyl,
provided that at least one of

Y_b and Z_b is sulfinyl or sulfonyl,

L is a leaving group, and

5 m^1 is an integer of 1 to 6.

11. A pharmaceutical composition which comprises the
compound of Claim 1 or a pharmaceutically acceptable
salt thereof and a pharmaceutically acceptable carrier
10 or excipient.
12. A process for preparing a pharmaceutical composition
which comprises admixing the compound of Claim 1 or a
pharmaceutically acceptable salt thereof with a
15 pharmaceutically acceptable carrier or excipient.
13. Use of the compound of Claim 1 or a pharmaceutically
acceptable salt thereof as a medicament.
- 20 14. Use of the compound of Claim 1 or a pharmaceutically
acceptable salt thereof as an inhibitor of matrix
metalloproteinases (MMP) or tumor necrosis factor α
(TNF α).
- 25 15. Use of the compound of Claim 1 or a pharmaceutically
acceptable salt thereof for manufacturing a medicament
for treating and/or preventing MMP- or TNF α -mediated
diseases.
- 30 16. A method for treating and/or preventing MMP- or TNF α -
mediated diseases which comprises administering the
compound of Claim 1 or a pharmaceutically acceptable
salt thereof to a human being or an animal.
- 35 17. Use of the compound of Claim 1 or a pharmaceutically

acceptable salt thereof for treating and/or preventing
MMP- or TNF α -mediated diseases.

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Declaration, Power Of Attorney and Petition

Page 1 of 5

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

THIOPYRAN COMPOUNDS AS INHIBITORS OF MMP

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☒ was filed as PCT international application

Number _____ PCT/JP00/00018 ✓

on _____ January 6, 2000 ,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
✓ PP8068	Australia	07/01/99	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
✓ PQ1702	Australia	19/07/99	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes <input type="checkbox"/> No

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Residence: _____

Citizen of: _____

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We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

_____ (Application Number)	_____ (Filing Date)
_____ (Application Number)	_____ (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
PCT/JP00/00018	January 6, 2000	_____
_____	_____	_____
_____	_____	_____

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Kiyoshi Taniguchi
NAME OF FIRST ~~SOME~~ INVENTOR

Kiyoshi Taniguchi
Signature of Inventor

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